(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 February 2005 (10.02.2005)

PCT

(10) International Publication Number
WO 2005/012326 A1

(51) International Patent Classification[7]: C07H 19/06

(21) International Application Number: PCT/JP2004/011312

(22) International Filing Date: 30 July 2004 (30.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/491,534 1 August 2003 (01.08.2003) US

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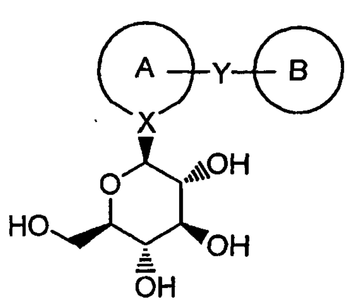
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL COMPOUNDS HAVING INHIBITORY ACTIVITY AGAINST SODIUM-DEPENDANT TRANSPORTER



(I)

(57) Abstract: A compound of the formula (I) wherein Ring A and Ring B are: (1) Ring A is an optionally substituted unsaturated monocyclic heterocyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring, (2) Ring A is an optionally substituted benzene ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring or an optionally substituted unsaturated fused heterobicyclic ring, or (3) Ring A is an optionally substituted unsaturated fused heterobicyclic ring, and Ring B are independently an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring; X is a carbon atom or a nitrogen atom; Y is -(CH2)n- (n is 1 or 2); a pharmaceutically acceptable salt thereof, or a prodrug thereof.

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DESCRIPTION

NOVEL COMPOUNDS HAVING INHIBITORY ACTIVITY AGAINST SODIUM-DEPENDANT TRANSPORTER

TECHNICAL FIELD

The present invention relates to a novel compound having an inhibitory activity against sodium-dependent glucose transporter (SGLT) being present in the intestine or kidney.

BACKGROUND ART

Although diet therapy and exercise therapy are essential in the treatment of diabetes mellitus, when these therapies do not sufficiently control the conditions of patients, insulin or an oral antidiabetic agent is additionally used. At the present, there have been used as an antidiabetic agent biguanide compounds, sulfonylurea compounds, insulin resistance improving agents and α-glucosidase inhibitors. However, these antidiabetic agents have various side effects. For example, biguanide compounds cause lactic acidosis, sulfonylurea compounds cause significant hypoglycemia, insulin resistance improving agents cause edema and heart failure, and α-glucosidase inhibitors cause abdominal bloating and diarrhea. Under such circumstances, it has been desired to develop novel drugs for treatment of diabetes mellitus having no such side effects.

Recently, it has been reported that hyperglycemia participates in the onset and progressive impairment of diabetes mellitus, i.e., glucose toxicity theory. Namely, chronic hyperglycemia leads to decrease insulin secretion and further to decrease insulin sensitivity, and as a result, the blood glucose concentration is increased so that diabetes mellitus is self-exacerbated [cf., Diabetologia, vol. 28, p.

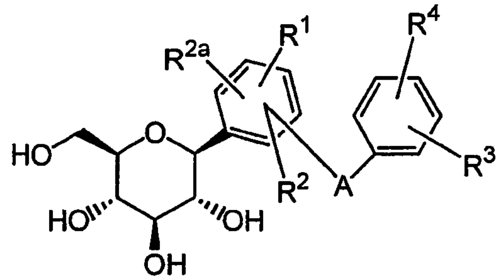
119 (1985); Diabetes Care, vol. 13, p. 610 (1990), etc.]. Therefore, by treating hyperglycemia, the aforementioned self-exacerbating cycle is interrupted so that the prophylaxis or treatment of diabetes mellitus is made possible.

As one of the methods for treating hyperglycemia, it is considered to excrete an excess amount of glucose directly into urine so that the blood glucose concentration is normalized. For example, by inhibiting sodium-dependent glucose transporter being present at the proximal convoluted tubule of kidney, the re-absorption of glucose at the kidney is inhibited, by which the excretion of glucose into urine is promoted so that the blood glucose level is decreased. In fact, it is confirmed that by continuous subcutaneous administration of phlorizin having SGLT inhibitory activity to diabetic animal models, hyperglycemia is normalized and the blood glucose level thereof can be kept normal for a long time so that the insulin secretion and insulin resistance are improved [cf., Journal of Clinical Investigation, vol. 79, p. 1510 (1987); ibid., vol. 80, p. 1037 (1987); ibid., vol. 87, p. 561 (1991), etc.].

In addition, by treating diabetic animal models with SGLT inhibitory agents for a long time, insulin secretion response and insulin sensitivity of the animals are improved without incurring any adverse affects on the kidney or imbalance in blood levels of electrolytes, and as a result, the onset and progress of diabetic nephropathy and diabetic neuropathy are prevented [cf., Journal of Medicinal Chemistry, vol. 42, p. 5311 (1999); British Journal of Pharmacology, vol. 132, p. 578 (2001), etc.].

From the above, SGLT inhibitors may be expected to improve insulin secretion and insulin resistance by decreasing the blood glucose level in diabetic patients and further prevent the onset and progress of diabetes mellitus and diabetic complications.

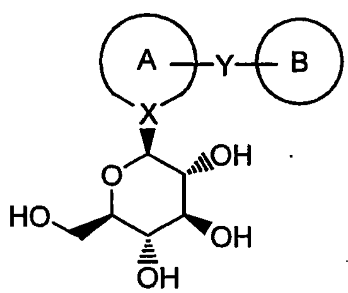
WO 01/27128 discloses an aryl C-glycoside compound having the following structure.



This compound is disclosed to be useful in the prophylaxis or treatment of diabetes mellitus, etc., as an SGLT inhibitor.

DISCLOSURE OF INVENTION

The present invention relates to a compound of the following formula I, or a pharmaceutically acceptable salt thereof, or a prodrug thereof.



(I)

wherein Ring A and Ring B are one of the followings: (1) Ring A is an optionally substituted unsaturated monocyclic heterocyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring, (2) Ring A is an optionally substituted benzene ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, or an optionally substituted unsaturated fused heterobicyclic ring wherein Y is linked to the heterocyclic ring of the fused heterobicyclic ring, or (3) Ring A is an optionally substituted unsaturated fused heterobicyclic ring, wherein the sugar moiety

X-(sugar) and the moiety -Y-(Ring B) are both on the same heterocyclic ring of the fused heterobicyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring;

X is a carbon atom or a nitrogen atom; and

Y is $-(CH_2)_n-$ (wherein n is 1 or 2).

The compound of the formula I exhibits an inhibitory activity against sodium-dependent glucose transporter being present in the intestine and the kidney of mammalian species, and is useful in the treatment of diabetes mellitus or diabetic complications such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, and delayed wound healing.

BEST MODE FOR CARRYING OUT THE INVENTION

Hereinafter, the present compound (I) is illustrated in more detail.

The definitions for each term used in the description of the present invention are listed below.

The "halogen atom" or the "halo" means chlorine, bromine, fluorine and iodine, and chlorine and fluorine are preferable.

The "alkyl group" means a straight or branched saturated monovalent hydrocarbon chain having 1 to 12 carbon atoms. The straight chain or branched chain alkyl group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkyl group having 1 to 4 carbon atoms is more preferable. Examples thereof are methyl group, ethyl group, propyl group, isopropyl group, butyl group, t-butyl group, isobutyl group, pentyl group, hexyl group, isohexyl group, heptyl group, 4,4-dimethylpentyl group, octyl group, 2,2,4-trimethylpentyl group, nonyl group, decyl group, and various branched chain isomers thereof. Further, the alkyl group may optionally and independently be substituted by 1 to 4 substituents as listed

below, if necessary.

The "alkylene group" or the "alkylene" means a straight or branched divalent saturated hydrocarbon chain having 1 to 12 carbon atoms. The straight chain or branched chain alkylene group having 1 to 6 carbon atoms is preferable, and the straight chain or branched chain alkylene group having 1 to 4 carbon atoms is more preferable. Examples thereof are methylene group, ethylene group, propylene group, trimethylene group, etc. If necessary, the alkylene group may optionally be substituted in the same manner as the above-mentioned "alkyl group".

Where alkylene groups as defined above attach at two different carbon atoms of the benzene ring, they form an annelated five, six or seven membered carbocycle together with the carbon atoms to which they are attached, and may optionally be substituted by one or more substituents defined below.

The "alkenyl group" means a straight or branched monovalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond. Preferable alkenyl group is a straight chain or branched chain alkenyl group having 1 to 6 carbon atoms, and the straight chain or branched chain alkenyl group having 1 to 4 carbon atoms is more preferable. Examples thereof are vinyl group, 2-propenyl group, 3-butenyl group, 2-butenyl group, 4-pentenyl group, 3-pentenyl group, 2-hexenyl group, 3-hexenyl group, 2-heptenyl group, 3-heptenyl group, 4-heptenyl group, 3-octenyl group, 3-nonenyl group, 4-decenyl group, 3-undecenyl group, 4-dodecenyl group, 4,8,12-tetradecatrienyl group, etc. The alkenyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The "alkenylene group" means a straight or branched divalent hydrocarbon chain having 2 to 12 carbon atoms and having at least one double bond. The straight chain or branched chain alkenylene group having 2 to 6 carbon atoms is preferable,

and the straight chain or branched chain alkenylene group having 2 to 4 carbon atoms is more preferable. Examples thereof are vinylene group, propenylene group, butadienylene group, etc. If necessary, the alkylene group may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary.

Where alkenylene groups as defined above attach at two different carbon atoms of the benzene ring, they form an annelated five, six or seven membered carbocycle (e.g., a fused benzene ring) together with the carbon atoms to which they are attached, and may optionally be substituted by one or more substituents defined below.

The "alkynyl group" means a straight or branched monovalent hydrocarbon chain having at least one triple bond. The preferable alkynyl group is a straight chain or branched chain alkynyl group having 1 to 6 carbon atoms, and the straight chain or branched chain alkynyl group having 1 to 4 carbon atoms is more preferable. Examples thereof are 2-propynyl group, 3-butynyl group, 2-butynyl group, 4-pentynyl group, 3-pentynyl group, 2-hexynyl group, 3-hexynyl group, 2-heptynyl group, 3-heptynyl group, 4-heptynyl group, 3-octynyl group, 3-nonynyl group, 4-decynyl group, 3-undecynyl group, 4-dodecynyl group, etc. The alkynyl group may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary.

The "cycloalkyl group" means a monocyclic or bicyclic monovalent saturated hydrocarbon ring having 3 to 12 carbon atoms, and the monocyclic saturated hydrocarbon group having 3 to 7 carbon atoms is more preferable. Examples thereof are a monocyclic alkyl group and a bicyclic alkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, cyclodecyl group, etc. These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned

below, if necessary. The cycloalkyl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The "cycloalkylidene group" means a monocyclic or bicyclic divalent saturated hydrocarbon ring having 3 to 12 carbon atoms, and the monocyclic saturated hydrocarbon group having 3 to 6 carbon atoms is preferable. Examples thereof are a monocyclic alkylidene group and a bicyclic alkylidene group such as cyclopropylidene group, cyclobutylidene group, cyclopentylidine group, cyclohexylidene group, etc. These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkylidene group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The "cycloalkenyl group" means a monocyclic or bicyclic monovalent unsaturated hydrocarbon ring having 4 to 12 carbon atoms and having at least one double bond. The preferable cycloalkenyl group is a monocyclic unsaturated hydrocarbon group having 4 to 7 carbon atoms. Examples thereof are monocyclic alkenyl groups such as cyclopentenyl group, cyclopentadienyl group, cyclohexenyl group, etc. These

groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkenyl group may optionally be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring and the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The "cycloalkynyl group" means a monocyclic or bicyclic unsaturated hydrocarbon ring having 6 to 12 carbon atoms, and having at least one triple bond. The preferable cycloalkynyl group is a monocyclic unsaturated hydrocarbon group having 6 to 8 carbon atoms. Examples thereof are monocyclic alkynyl groups such as cyclooctynyl group, cyclodecynyl group. These groups may optionally be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the cycloalkynyl group may optionally and independently be condensed with a saturated hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The "aryl group" means a monocyclic or bicyclic monovalent aromatic hydrocarbon group having 6 to 10 carbon atoms. Examples thereof are phenyl group, naphthyl group (including 1-naphthyl group and 2-naphthyl group). These groups may optionally and independently be substituted by 1 to 4 substituents as mentioned below, if necessary. Besides, the aryl group may optionally be condensed with a saturated

hydrocarbon ring or an unsaturated hydrocarbon ring (said saturated hydrocarbon ring and unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO or SO_2 within the ring, if necessary), and the condensed saturated hydrocarbon ring or the unsaturated hydrocarbon ring may be optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The "unsaturated monocyclic heterocyclic ring" means an unsaturated hydrocarbon ring containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the preferable one is a 4- to 7-membered saturated or unsaturated hydrocarbon ring containing 1-4 heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom. Examples thereof are pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, 4,5-dihydrooxazole, thiazole, isothiazole, thiadiazole, triazole, tetrazole, etc. Among them, pyridine, pyrimidine, pyrazine, furan, thiophene, pyrrole, imidazole, oxazole, and thiazole can be preferably used. The "unsaturated monocyclic heterocyclic ring" may optionally and independently be substituted by 1-4 substituents as mentioned below, if necessary.

The "unsaturated fused heterobicyclic ring" means hydrocarbon ring comprised of a saturated or a unsaturated hydrocarbon ring condensed with the above mentioned unsaturated monocyclic heterocyclic ring where said saturated hydrocarbon ring and said unsaturated hydrocarbon ring may optionally contain an oxygen atom, a nitrogen atom, a sulfur atom, SO, or SO_2 within the ring, if necessary. The "unsaturated fused heterobicyclic ring" includes, for example, benzothiophene, indole, tetrahydrobenzothiophene, benzofuran, isoquinoline, thienothiophene, thienopyridine, quinoline, indoline, isoindoline, benzothiazole, benzoxazole, indazole, dihydro-

isoquinoline, etc. Further, the "heterocyclic ring" also includes possible N- or S-oxides thereof.

The "heterocyclyl" means a monovalent group of the above-mentioned unsaturated monocyclic heterocyclic ring or unsaturated fused heterobicyclic ring and a monovalent group of the saturated version of the above-mentioned unsaturated monocyclic heterocyclic or unsaturated fused heterobicyclic ring. If necessary, the heterocyclyl may optionally and independently be substituted by 1 to 4 substituents as mentioned below.

The "alkanoyl group" means a formyl group and ones formed by binding an "alkyl group" to a carbonyl group.

The "alkoxy group" means ones formed by binding an "alkyl group" to an oxygen atom.

The substituent for the above each group includes, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro group, a cyano group, an oxo group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an

alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenyl-sulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cyclo-alkenylsulfonyl group, a cycloalkynylsulfonyl group, an aryl-sulfonyl group, and a heterocyclylsulfonyl group. Each group as mentioned above may optionally be substituted by these substituents.

Further, the terms such as a haloalkyl group, a halo-lower alkyl group, a haloalkoxy group, a halo-lower alkoxy group, a halophenyl group, or a haloheterocyclyl group mean an alkyl group, a lower alkyl group, an alkoxy group, a lower alkoxy group, a phenyl group or a heterocyclyl group (hereinafter, referred to as an alkyl group, etc.) being substituted by one or more halogen atoms, respectively. Preferable ones are an alkyl group, etc. being substituted by 1 to 7 halogen atoms, and more preferable ones are an alkyl group, etc. being substituted by 1 to 5 halogen atoms. Similarly, the terms such as a hydroxyalkyl group, a hydroxy-lower alkyl group, a hydroxy-

alkoxy group, a hydroxy-lower alkoxy group and a hydroxyphenyl group mean an alkyl group, etc., being substituted by one or more hydroxy groups. Preferable ones are an alkyl group, etc., being substituted by 1 to 4 hydroxy groups, and more preferable ones are an alkyl group, etc., being substituted by 1 to 2 hydroxy groups. Further, the terms such as an alkoxyalkyl group, a lower alkoxyalkyl group, an alkoxy-lower alkyl group, a lower alkoxy-lower alkyl group, an alkoxyalkoxy group, a lower alkoxyalkoxy group, an alkoxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, an alkoxyphenyl group, and a lower alkoxyphenyl group means an alkyl group, etc., being substituted by one or more alkoxy groups. Preferable ones are an alkyl group, etc., being substituted by 1 to 4 alkoxy groups, and more preferable ones are an alkyl group, etc., being substituted by 1 to 2 alkoxy groups.

The terms "arylakyl" and "arylalkoxy" as used alone or as part of another group refer to alkyl and alkoxy groups as described above having an aryl substituent.

The term "lower" used in the definitions for the formulae in the present specification means a straight or branched carbon chain having 1 to 6 carbon atoms, unless defined otherwise. More preferably, it means a straight or branched carbon chain having 1 to 4 carbon atoms.

The "prodrug" means an ester or carbonate, which is formed by reacting one or more hydroxy groups of the compound of the formula I with an acylating agent substituted by an alkyl, an alkoxy or an aryl by a conventional method to produce acetate, pivalate, methylcarbonate, benzoate, etc. Further, the prodrug includes also an ester or amide, which is similarly formed by reacting one or more hydroxy groups of the compound of the formula I with am α-amino acid or a β-amino acid, etc. using a condensing agent by a conventional method.

The pharmaceutically acceptable salt of the compound of

the formula I includes, for example, a salt with an alkali metal such as lithium, sodium, potassium, etc.; a salt with an alkaline earth metal such as calcium, magnesium, etc.; a salt with zinc or aluminum; a salt with an organic base such as ammonium, choline, diethanolamine, lysine, ethylenediamine, t-butylamine, t-octylamine, tris(hydroxymethyl)aminomethane, N-methyl glucosamine, triethanolamine and dehydroabietylamine; a salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, etc.; or a salt with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, etc.; or a salt with an acidic amino acid such as aspartic acid, glutamic acid, etc.

The compound of the present invention also includes a mixture of stereoisomers, or each pure or substantially pure isomer. For example, the present compound may optionally have one or more asymmetric centers at a carbon atom containing any one of substituents. Therefore, the compound of the formula I may exist in the form of enantiomer or diastereomer, or a mixture thereof. When the present compound (I) contains a double bond, the present compound may exist in the form of geometric isomerism (cis-compound, trans-compound), and when the present compound (I) contains an unsaturated bond such as carbonyl, then the present compound may exist in the form of a tautomer, and the present compound also includes these isomers or a mixture thereof. The starting compound in the form of a racemic mixture, enantiomer or diastereomer may be used in the processes for preparing the present compound. When the present compound is obtained in the form of a diastereomer or enantiomer, they can be separated by a conventional method such as

chromatography or fractional crystallization.

In addition, the present compound (I) includes an intramolecular salt, hydrate, solvate or polymorphism thereof.

The optionally substituted unsaturated monocyclic heterocyclic ring of the present invention is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxyl group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an

alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenyl-sulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group wherein each substituent may optionally be further substituted by these substituents.

The optionally substituted unsaturated fused heterobicyclic ring of the present invention is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidene- methyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenyl- carbonyl group, a cycloalkynyl- carbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxy- carbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxy- carbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl

group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cyclo- alkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cyclo- alkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclyl- carbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoyl- amino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkyl- sulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cyclo- alkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cyclo- alkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group, wherein each substituent may optionally be further substituted by these substituents.

The optionally substituted benzene ring of the present invention is a benzene ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a

cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group, an alkylene group, an alkyleneoxy group, an alkylenedioxy group, and an alkenylene group wherein each substituent may optionally be further substituted by these

substituents. Moreover, the optionally substituted benzene ring includes a benzene ring substituted with an alkylene group to form an annelated carbocycle together with the carbon atoms to which they are attached, and also includes a benzene ring substituted with an alkenylene group to form an annelated carbocycle such as a fused benzene ring together with the carbon atoms to which they are attached.

The optionally substituted unsaturated monocyclic heterocyclic ring is preferably an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, and an oxo group.

The optionally substituted unsaturated fused heterobicyclic ring is preferably an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cyclo-

alkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, and an oxo group.

The optionally substituted benzene ring is preferably a benzene ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, an alkylene group, an alkyleneoxy group, an alkylenedioxy group, and an alkenylene group.

In another preferable embodiment, the optionally substituted unsaturated monocyclic heterocyclic ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl

group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkyl- sulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, phenylsulfonyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group,

a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

wherein each of the above-mentioned substituents on the unsaturated monocyclic heterocyclic ring, the unsaturated fused heterobicyclic ring and the benzene ring may further be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, a mono- or di-alkylamino group, a carboxyl group, an alkoxycarbonyl group, a phenyl group, an alkyleneoxy group, an alkylenedioxy group, and an oxo group.

As a preferable embodiment, there is mentioned a compound in which the optionally substituted unsaturated monocyclic heterocyclic ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group,

an alkoxycarbonylamino group, a carboxy group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

wherein each of the above-mentioned substituents on the unsaturated monocyclic heterocyclic ring, the unsaturated fused heterobicyclic ring and the benzene ring may further be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, a mono- or di-alkylamino group, a carboxyl group, a hydroxy group, a phenyl group, an alkylenedioxy group, an alkyleneoxy group, and an alkoxycarbonyl group.

As another preferable embodiments, there are mentioned (1) a compound in which Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group,

a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group, and

Ring B is an unsaturated monocyclic heterocyclic ring, an unsaturated fused heterobicyclic ring, or a benzene ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkl-sulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

(2) a compound in which Ring A is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group,

and

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group and an oxo group; and

(3) a compound in which Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group, and

Ring B is an unsaturated monocyclic heterocyclic ring, an unsaturated fused heterobicyclic ring, or a benzene ring, each of which may optionally be substituted by 1-3 substituents,

independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkl-sulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group and an oxo group;

wherein each of the above-mentioned substituents on Ring A and Ring B may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, a mono- or di-alkylamino group, a carboxyl group, a hydroxy group, a phenyl group, an alkylenedioxy group, an alkyleneoxy group, and an alkoxycarbonyl group.

As more preferable embodiments, there is mentioned a compound in which Ring A and Ring B are

(1) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or an oxo group, and Ring B is (a) a benzene ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom,

a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; (b) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or (c) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group;

(2) Ring A is a benzene ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a phenyl group, or a lower alkenylene group, and Ring B is (a) an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a phenyl-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl

group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; (b) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or

(3) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or an oxo group, and Ring B is (a) a benzene ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; (b) an unsaturated monocyclic heterocyclic ring which may optionally

be substituted by a halogen atom; a cyano group; a lower alkyl group; a halo-lower alkyl group; a lower alkoxy group; a halo-lower alkoxy group; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; or (c) an unsaturated fused heterobicyclic ring which may optionally be substituted by a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a mo- or di-lower alkylamino group, a phenyl group which may be substituted with a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group; and a heterocyclyl group which may optionally be substituted with a group selected from a halogen atom, cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a mono- or di-lower alkylamino group.

In another preferable embodiment, there is mentioned a compound of the formula I, wherein Y is $-CH_2-$ and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is a benzene ring which is substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a phenyl group, and a lower alkenylene group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy

group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxy phenyl group, a lower alkylenedioxyphenyl group, a lower alkyleneoxy phenyl group, a mono- or di-lower alkylaminophenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, a lower alkoxyheterocyclyl group, and a mono- or di-lower alkylaminoheterocycyclyl group.

In yet another preferable embodiment, there is mentioned a compound of the formula I wherein Y is $-CH_2-$ and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halogen atom, a lower alkoxy group, and an oxo group, and Ring B is a benzene ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, , a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a heterocyclyl group, a haloheterocyclyl group, and a lower alkylheterocyclyl group.

Further, as another preferable embodiment, there is mentioned a compound of formula I wherein Y is $-CH_2-$ and is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halogen atom, a lower alkoxy group, and an oxo group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may be substituted by 1-3 substituents selected from the group consisting of a lower

alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxyphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, a lower alkoxyheterocyclyl group, and a lower alkoxyheterocyclyl group

As a more preferable compound, a compound in which X is a carbon atom and Y is $-CH_2-$ is mentioned.

Further, as another preferable compound, there is mentioned a compound in which Ring A and Ring B are

(1) Ring A is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a halogen atom or a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, a phenyl group, and a lower alkenylene group, and

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and an oxo group,

(2) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group, and
Ring B is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a lower alkylene group,

(3) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a halogen atom or a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,
Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally

substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and an oxo group;

(4) Ring A is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,

Ring B is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and a lower alkylene group, or

(5) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted by a lower alkoxy group, a lower alkoxy group optionally substituted by

a halogen atom or a lower alkoxy group, a cycloalkyl group, a cycloalkoxy group, and an oxo group,
Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group or a phenyl group; a lower alkoxy group optionally substituted by a halogen atom or a lower alkoxy group; a cycloalkyl group; a cycloalkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; and an oxo group.

Preferred is a compound wherein Y is linked at the 3-position of Ring A, with respect to X being the 1-position, Ring A is a benzene ring which may optionally be substituted by a halogen atom, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group, or a phenyl group, and Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom or a phenyl group; a lower alkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; and an oxo group.

Preferred is a compound wherein Y is linked at the

3-position of Ring A, with respect to X being the 1-position, Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by a substituent selected from a halogen atom, a lower alkyl group, and an oxo group, and Ring B is a benzene ring which may optionally be substituted by a substituent selected from the group consisting of a halogen atom; a lower alkyl group optionally substituted by a halogen atom or a phenyl group; a lower alkoxy group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group; and a lower alkylene group.

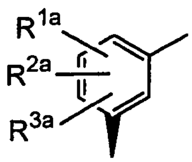
Preferable unsaturated monocyclic heterocyclic ring includes a 5- or 6-membered unsaturated heterocyclic ring containing 1 or 2 hetero atoms independently selected from a nitrogen atom, an oxygen atom, and a sulfur atom. More specifically, preferred are furan, thiophene, oxazole, isoxazole, triazole, tetrazole, pyrazole, pyridine, pyrimidine, pyrazine, dihydroisoxazole, dihydropyridine and tetrazole. Preferable unsaturated fused heterobicyclic ring includes a 9- or 10-membered unsaturated fused heterocyclic ring containing 1 to 4 hetero atoms independently selected from a nitrogen atom, an oxygen atom, and a sulfur atom. More specifically, preferred are indoline, isoindoline, benzothiazole, benzoxazole, indole, indazole, quinoline, isoquinoline, benzothiophene, benzofuran, thienothiophene, and dihydroisoquinoline.

More preferred compounds include a compound wherein Ring A is a benzene ring which may optionally be substituted by a substituent selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a phenyl group, and Ring B is a heterocyclic ring

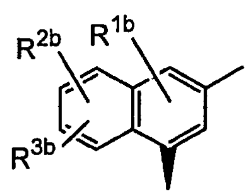
selected from the group consisting of thiophene, furan, benzofuran, benzothiophene, and benzothiazole, wherein the heterocyclic ring may optionally be substituted by a substituent selected from the following group: a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a lower alkylphenyl group, a lower alkoxyphenyl group, a thienyl group, a halothienyl group, a pyridyl group, a halopyridyl group, and a thiazolyl group.

Another preferred compounds include a compound wherein Y is $-CH_2-$, Ring A is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring selected from the group consisting of thiophene, dihydroisoquinoline, dihydroisoxazole, triazole, pyrazole, dihydropyridine, dihydroindole, indole, indazole, pyridine, pyrimidine, pyrazine, quinoline, and a isoindoline, wherein the heterocyclic ring may optionally substituted by a substituent selected from the following group: a halogen atom, a lower alkyl group, and an oxo group, and Ring B is a benzene ring which may optionally be substituted by a substituent selected from the following group: a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, and a halo-lower alkoxy group.

Further, a preferable compound of the formula I includes a compound wherein Ring A is



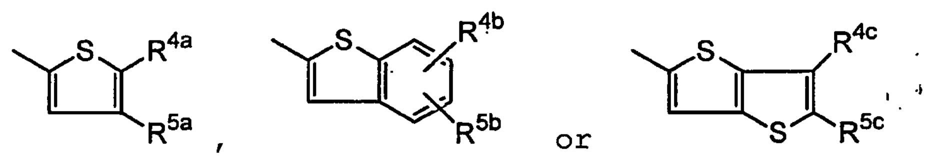
or



wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a

hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, a phenyl group, a phenylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or a phenylsulfonyl group, and

Ring B is



wherein R^{4a} and R^{5a} are each independently a hydrogen atom; a halogen atom; a hydroxy group; an alkoxy group; an alkyl group; a haloalkyl group; a haloalkoxy group; a hydroxyalkyl group; an alkoxyalkyl group; a phenylalkyl group; an alkoxyalkoxy group; a hydroxyalkoxy group; an alkenyl group; an alkynyl group; a cycloalkyl group; a cycloalkylidenemethyl group; a cycloalkenyl group; a cycloalkyloxy group; a phenyloxy group; a phenylalkoxy group; a cyano group; a nitro group; an amino group; a mono- or di-alkylamino group; an alkanoylamino group; a carboxyl group; an alkoxycarbonyl group; a carbamoyl group; a mono- or di-alkylcarbamoyl group; an alkanoyl group; an alkylsulfonylamino group; a phenylsulfonylamino group; an alkylsulfinyl group; an alkylsulfonyl group; a phenylsulfonyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkylenedioxy group, an alkyleneoxy group, or a mono- or di-alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group,

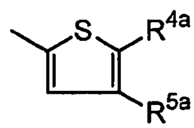
an alkyl group, a haloalkyl group, an alkoxy group or a haloalkoxy group, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form an alkylene group; and R^{4b}, R^{5b}, R^{4c} and R^{5c} are each independently a hydrogen atom; a halogen atom; a hydroxy group; an alkoxy group; an alkyl group; a haloalkyl group; a haloalkoxy group; a hydroxyalkyl group; an alkoxyalkyl group; a phenylalkyl group; an alkoxyalkoxy group; a hydroxyalkoxy group; an alkenyl group; an alkynyl group; a cycloalkyl group; a cycloalkylidenemethyl group; a cycloalkenyl group; a cycloalkyloxy group; a phenyloxy group; a phenylalkoxy group; a cyano group; a nitro group; an amino group; a mono- or di-alkylamino group; an alkanoylamino group; a carboxyl group; an alkoxycarbonyl group; a carbamoyl group; a mono- or di-alkylcarbamoyl group; an alkanoyl group; an alkylsulfonylamino group; a phenylsulfonylamino group; an alkylsulfinyl group; an alkylsulfonyl group; a phenylsulfonyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, a methylenedioxy group, an ethyleneoxy group, or a mono- or di-alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group or a haloalkoxy group.

More preferred is a compound wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a phenyl group;
R^{4a} and R^{5a} are each independently a hydrogen atom; a halogen atom; a lower alkyl group; a halo-lower alkyl group; a phenyl-lower alkyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, or

a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form a lower alkylene group; and

R^{4b}, R^{5b}, R^{4c} and R^{5c} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group.

Further preferred is a compound in which Ring B is



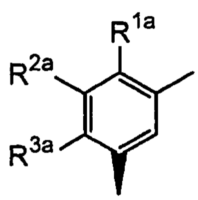
,

wherein R^{4a} is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group, and

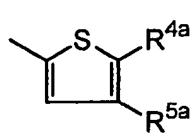
R^{5a} is a hydrogen atom, or

R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form a lower alkylene group.

Further more preferred is a compound in which Ring A is



wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms; and Ring B is

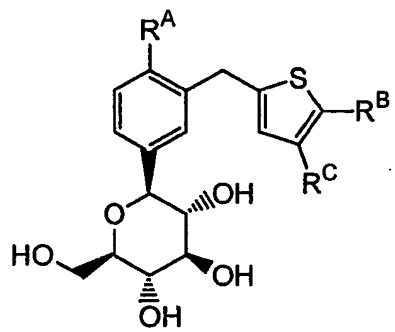


,

wherein R^{4a} is a phenyl group optionally substituted by a

substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group, and R^{5a} is a hydrogen atom, and Y is $-CH_2-$.

In another preferable embodiment of the present invention, a preferable compound can be represented by the following formula IA:



(IA)

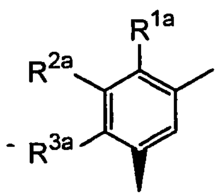
wherein R^A is a halogen atom, a lower alkyl group or a lower alkoxy group; R^B is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, or a mono- or di-lower alkylamino group; and R^C is hydrogen atom; or R^B and R^C taken together are a fused benzene ring which may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group.

Among them, a compound in which R^B is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group or a halo-lower alkoxy group; or a heterocyclyl group optionally

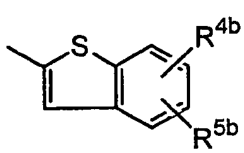
substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group is preferred.

A preferred heterocyclyl group includes a 5- or 6-membered heterocyclyl group containing 1 or 2 hetero atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom, or a 9- or 10-membered heterocyclyl group containing 1 to 4 hetero atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom. Specifically, a thienyl group, a pyridyl group, a pyrimidyl group, a pyrazinyl group, pyrazolyl group, a thiazolyl group, a quinolyl group, and a tetrazolyl group are preferred.

In another preferable embodiment of the present invention, preferred is a compound in which Ring A is

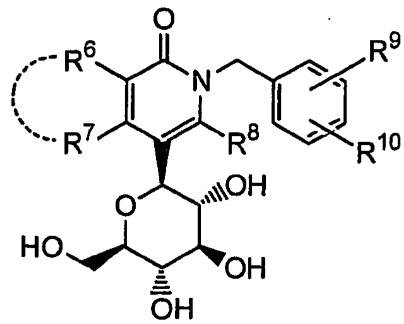


wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms; and Ring B is



wherein R^{4b} and R^{5b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group.

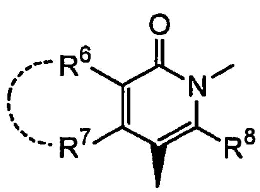
Another preferable embodiment includes a compound represented by the following formula IB:



(IB)

wherein R^8, R^9 and R^{10} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkylcarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or an arylsulfonyl group; and

a group represented by:



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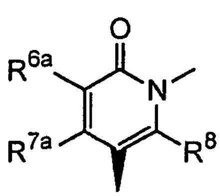
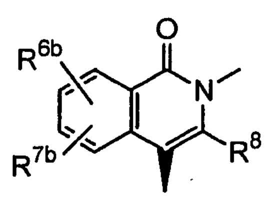


or

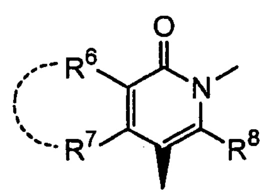


,

wherein R^{6a} and R^{7a} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group,

an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkylcarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or an arylsulfonyl group and R^{6b} and R^{7b} are each independently a hydrogen atom, a halogen atom, an alkyl group, a haloalkyl group, or an alkoxy group.

Among the compounds represented by the formula IB, more preferred is a compound in which R^8, R^9 and R^{10} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a cycloalkyl group, a hydroxy-lower alkyl group, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a cycloalkoxy group, a halo-lower alkoxy group, or a lower alkoxy-lower alkoxy group, and a group represented by:



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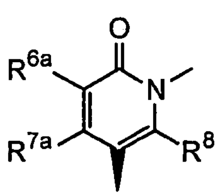
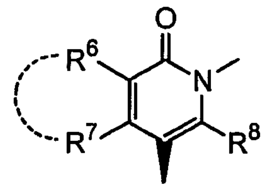


wherein R^{6a}, R^{7a} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a cycloalkyl group, a hydroxy-lower alkyl group, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a cycloalkoxy group, a

halo-lower alkoxy group, or a lower alkoxy-lower alkoxy group, or a group represented by:



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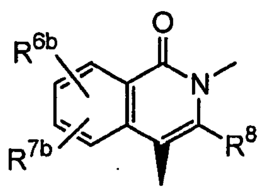
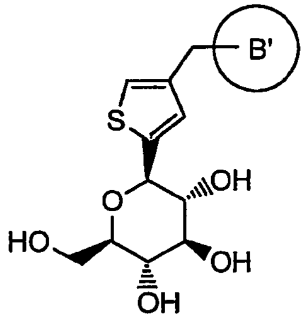


wherein R^{6b} and R^{7b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, or a lower alkoxy group.

Another preferable embodiment includes a compound represented by the following formula IC:



(IC)

Wherein Ring B′ is an optionally substituted benzene ring, an optionally substituted unsaturated monocyclic heterocyclic ring, or an optionally substituted unsaturated fused heterobicyclic ring.

Preferable examples of Ring B′ include a benzene ring and a heterocyclic ring, both of which may have a substituent(s) selected from the group consisting of a halogen atom; a cyano group; a lower alkyl group optionally substituted by a halogen atom; a lower alkoxy group optionally substituted by a halogen atom; a lower alkanoyl group; a mono- or di-lower alkylamino group; a lower alkoxycarbonyl group; a carbamoyl group; a mono-

or di-lower alkylcarbamoyl group; a phenyl group optionally substituted by a substituent(s) selected from a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom, a lower alkanoyl group, a mono- or di-lower alkylamino group, a lower alkoxycarbonyl group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; a heterocyclyl group optionally substituted by a substituent(s) selected from a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom, a lower alkanoyl group, a mono- or di-lower alkylamino group, a lower alkoxycarbonyl group, a carbamoyl group, or a mono- or di-lower alkylcarbamoyl group; an alkylene group; and an oxo group.

More preferable examples of Ring B′ include a benzene ring which may be substituted by a substituent selected from the group consisting of a halogen atom; a cyano group; a lower alkyl group optionally substituted by a halogen atom; a lower alkoxy group optionally substituted by a halogen atom; a mono- or di-lower alkylamino group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom; a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group optionally substituted by a halogen atom, a lower alkoxy group optionally substituted by a halogen atom.

Preferred compound of the present invention may be selected from the following group:

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethylbenzo[b]thiophen-2-ylmethyl)benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(5-thiazolyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-(5-phenyl-2-thienyl-

methyl)benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(2-pyrimidinyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(2-pyrimidinyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-difluoromethyl-phenyl)-2-thienylmethyl]benzene;

the pharmaceutically acceptable salt thereof; and

the prodrug thereof.

The compound (I) of the present invention exhibits an excellent inhibitory activity against sodium-dependent glucose transporter, and an excellent blood glucose lowering effect. Therefore, the compound of the present invention is useful in the treatment or the prophylaxis of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.) or diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, or is useful in the treatment of postprandial hyperglycemia.

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparation for oral administration includes,

for example, solid preparation such as tablets, granules, capsules, powders, etc., or solution preparations, suspension preparations, or emulsion preparations, etc. Suitable pharmaceutical preparation for parenteral administration includes, for example, suppositories; injection preparations and intravenous drip preparations using distilled water for injection, physiological saline solution or aqueous glucose solution; or inhalant preparations.

The dosage of the present compound (I) or a pharmaceutically acceptable salt thereof may vary according to the administration routes, ages, body weight, conditions of a patient, or kinds and severity of a disease to be treated, and it is usually in the range of about 0.1 to 50 mg/kg/day, preferably in the range of about 0.1 to 30 mg/kg/day.

The compound of the formula I may be used, if necessary, in combination with one or more of other antidiabetic agents and/or one or more agents for treatment of other diseases. The present compound and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The other antidiabetic agents include, for example, antidiabetic or antihyperglycemic agents including insulin, insulin secretagogues, or insulin sensitizers, or other antidiabetic agents having an action mechanism different from SGLT inhibition, and 1, 2, 3 or 4 of these other antidiabetic agents may preferably be used. Concrete examples thereof are biguanide compounds, sulfonylurea compounds, α-glucosidase inhibitors, PPARγ agonists (e.g., thiazolidinedione compounds), PPARα/γ dual agonists, dipeptidyl peptidase IV (DPP4) inhibitors, mitiglinide compounds, and/or nateglinide compounds, and insulin, glucagon-like peptide-1 (GLP-1), PTP1B inhibitors, glycogen phosphorylase inhibitors, RXR modulators, and/or glucose 6-phosphatase inhibitors.

The agents for treatment of other diseases include, for example, an anti-obesity agent, an antihypertensive agent, an antiplatelet agent, an anti-atherosclerotic agent and/or a hypolipidemic agent.

The SGLT inhibitors of the formula I may be used in combination with agents for treatment of diabetic complications, if necessary. These agents include, for example, PKC inhibitors and/or ACE inhibitors.

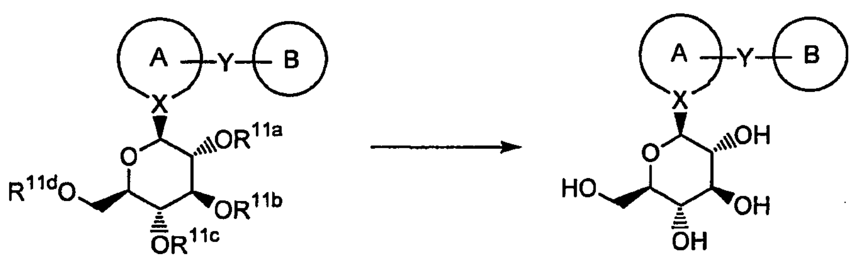
The dosage of those agents may vary according to ages, body weight, and conditions of patients, and administration routes, dosage forms, etc.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, dogs, etc., for example, in the dosage form of tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The present compound of the formula I may be prepared by the following Processes.

Process 1

The compound of the formula I may be prepared by a method as shown in the following scheme:



(II) (I)

wherein R^{11a} is a hydrogen atom or a protecting group for a hydroxy group, and R^{11b}, R^{11c} and R^{11d} are each independently a protecting group for a hydroxy group, and other symbols are as defined

above.

The compound of the formula I may be prepared by deprotecting the compound of the formula II.

In the compound of the formula II, the protecting group for hydroxy group may be any conventional protecting groups, and a benzyl group, an acetyl group, and an alkylsily group such as a trimethylsilyl group may be used. Further, the protecting group for hydroxy group may form acetal or silylacetal together with adjacent hydroxy groups. Examples of such protecting group include an alkylidene group such as an isopropylidene group, a sec-butylidene group, etc., a benzylidene group, or a dialkylsilylene group such as di-tert-butylsilylene group, etc., which can be formed, for example, by combining R^{11c} and R^{11d} at the terminal thereof.

The deprotection can be carried out according to the kinds of protecting group to be removed, for example, by conventional processes such as reduction, hydrolysis, acid treatment, fluoride treatment, etc.

For example, when a benzyl group is to be removed, the deprotection can be carried out by (1) catalytic reduction using a palladium catalyst (e.g., palladium-carbon, palladium hydroxide) under hydrogen atmosphere in a suitable solvent (e.g., methanol, ethanol, ethyl acetate); (2) treatment with an dealkylating agent such as boron tribromide, boron trichloride, boron trichloride · dimethylsulfide complex, or iodotrimethylsilane in a suitable solvent (e.g., dichloromethane); or (3) treatment with a lower alkylthiol such as ethanethiol in the presence of a Lewis acid (e.g., boron trifluoride · diethyl ether complex) in a suitable solvent (e.g., dichloromethane).

When a protecting group is removed by hydrolysis, the hydrolysis can be carried out by treating the compound of formula II with a base (e.g., sodium hydroxide, potassium

hydroxide, lithium hydroxide, sodium methoxide, sodium ethoxide, etc.) in a suitable solvent (e.g., tetrahydrofuran, dioxane, methanol, ethanol, water, etc.).

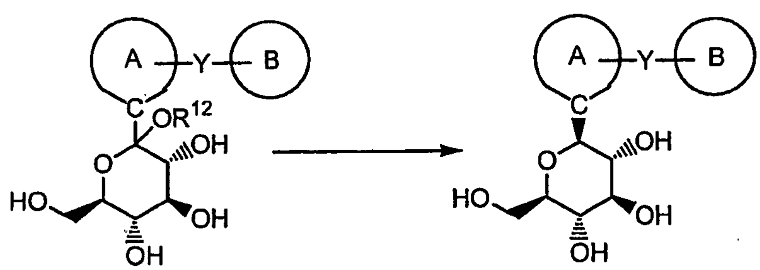
Acid treatment can be carried out by treating the compound of formula II with an acid (e.g., hydrochloric acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc.) in a suitable solvent (e.g., methanol, ethanol, etc.).

In case of the fluoride treatment, it can be carried out by treating the compound of formula II with a fluoride (e.g., hydrogen fluoride, hydrogen fluoride-pyridine, tetrabutylammonium fluoride, etc.) in a suitable solvent (e.g., acetic acid, a lower alcohol (methanol, ethanol, etc.), acetonitrile, tetrahydrofuran, etc.).

The deprotection reaction can be preferably carried out under cooling or with heating, for example, at a temperature of from 0°C to 50°C, more preferably at a temperature of from 0°C to room temperature.

Process 2

The compound of the formula I wherein X is a carbon atom may be prepared by a method as shown in the following scheme:



(III) (I-a)

wherein R^{12} is a lower alkyl group, and other symbols are as defined above.

The compound of the formula I-a may be prepared by reducing the compound of the formula III.

The reduction can be carried out by treatment with a silane

reagent, in the presence of an acid, in a suitable solvent or in the absence of a solvent.

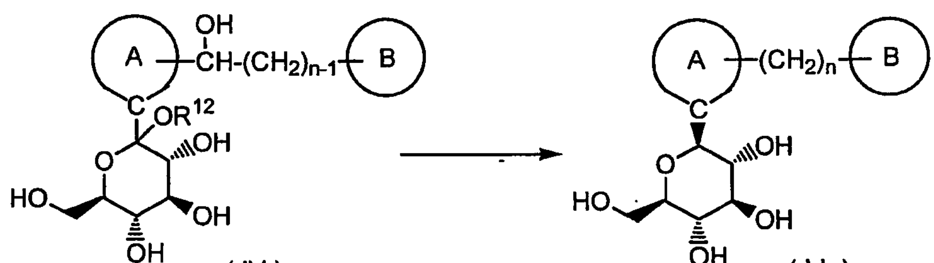
As the acid, for example, a Lewis acid such as boron trifluoride · diethyl ether complex, titanium tetrachloride, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc., may preferably be used.

As the silane reagent, for example, a trialkylsilane such as triethylsilane, triisopropylsilane, etc. may preferably be used.

As the solvent, any kinds of solvent may be used as long as it does not affect the reaction, and for example, acetonitrile, dichloromethane, or an acetonitrile/dichloromethane mixture may preferably be used.

Process 3

The compound of the formula I wherein X is a carbon atom may be prepared by a method as shown in the following scheme:



(IV) (I-b)

wherein the symbols are as defined above.

Namely, the compound of the formula I-b may be prepared by reducing the compound of the formula IV.

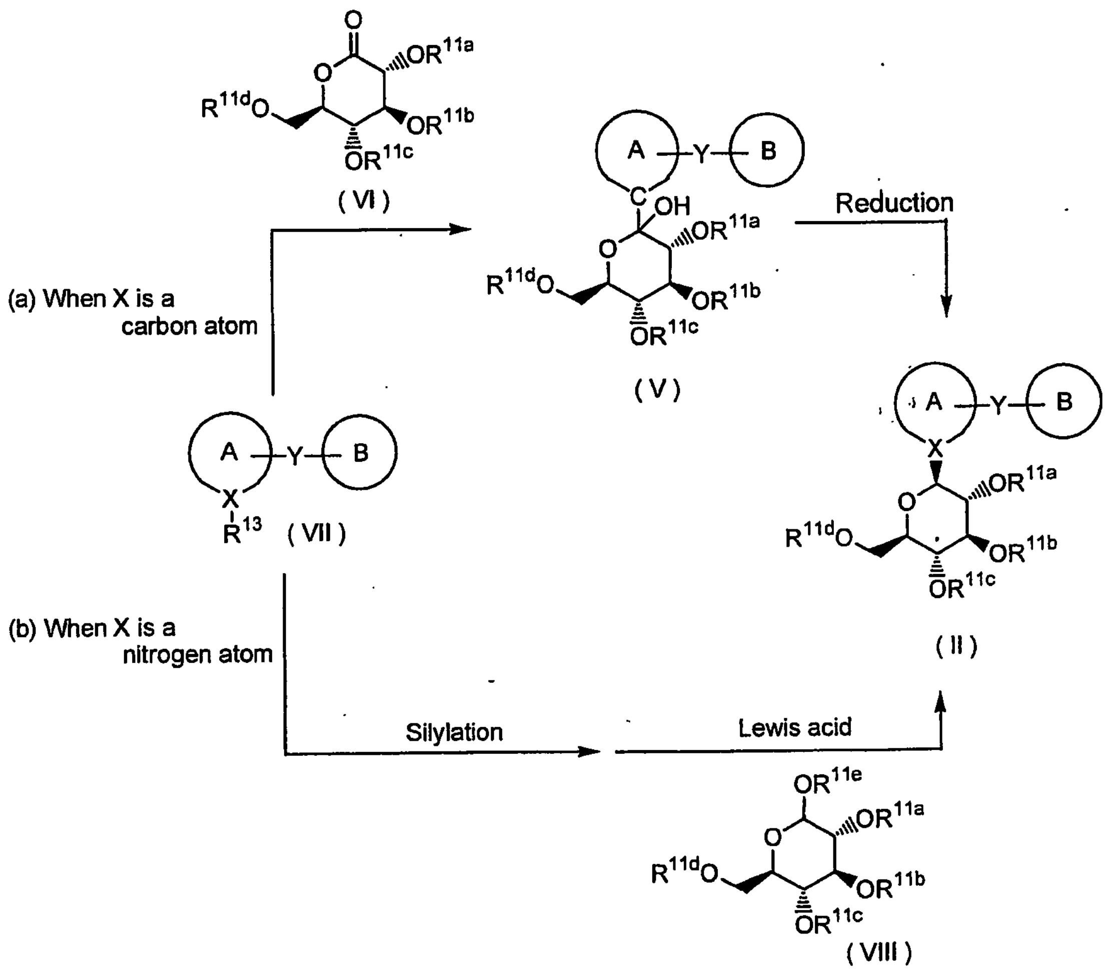
The reduction can be carried out in a manner similar to Process 2. In other words, it can be carried out by treatment with a silane reagent (e.g., triethylsilane, etc.), in the presence of a Lewis acid (e.g., boron trifluoride · diethyl ether complex, etc.), in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.).

The compound of the present invention thus obtained may be isolated and purified by a conventional method well known

in the organic synthetic chemistry such as recrystallization, column chromatography, etc.

The starting compound represented by the formula (II), (III) or (IV) may be prepared by either one of the following steps (a) - (j).

Steps (a) and (b):



In the above scheme, R^{13} is (1) a bromine atom or an iodine atom when X is a carbon atom; or (2) a hydrogen atom when X is a nitrogen atom, R^{11e} is a protecting group for hydroxy group, and the other symbols are as defined above.

Step (a):

Among the compounds of the formula II, the compound wherein X is a carbon atom may be prepared by coupling the compound of the formula VII with the compound of the formula

VI to give the compound of formula V, followed by reduction of the compound of the formula V.

The coupling reaction can be carried out by lithiating the compound of the formula VII, followed by reacting the resultant with the compound of the formula VI.

In particular, the compound of the formula VII can be treated with an alkyllithium, followed by reacting the resultant with the compound of the formula VI. As the alkyllithium, methyl lithium, n-butyl lithium, t-butyl lithium, etc. are preferably used. The solvent may be any solvent which does not disturb the reaction, and ethers such as tetrahydrofuran, diethyl ether, etc., are preferably used. This reaction can be carried out from under cooling (e.g., at -78°C) to room temperature.

The reduction can be carried out in a manner similar to Process 2. Namely, it can be carried out by treating the compound of formula V with a silane reagent (e.g., triethylsilane, etc.) in the presence of a Lewis acid (e.g., boron trifluoride · diethyl ether complex, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.).

Step (b)

Among the compounds of the formula II, the compound wherein X is a nitrogen atom may be prepared by silylating the compound of the formula VII in a solvent, followed by reacting the resultant with the compound of the formula VIII (e.g., an α- or β-D-glucose pentaacetate, etc.) in the presence of a Lewis acid.

The silylation reaction can be carried out by treating the compound of formula VII with a silylating agent in a solvent. The silylating agent includes, for example, N,O-bis(trimethylsilyl)acetamide, 1,1,1,3,3,3-hexamethyldisilazane, etc.

The solvent may be, for example, halogenated hydrocarbons

such as dichloromethane, dichloroethane, chloroform, etc., ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, etc., acetonitrile, etc.

This reaction is preferably carried out under cooling or with heating, for example, at a temperature of from 0°C to 60°C, preferably at a temperature of from room temperature to 60°C.

The reaction with the compound of the formula VIII can be carried out in a solvent in the presence of a Lewis acid.

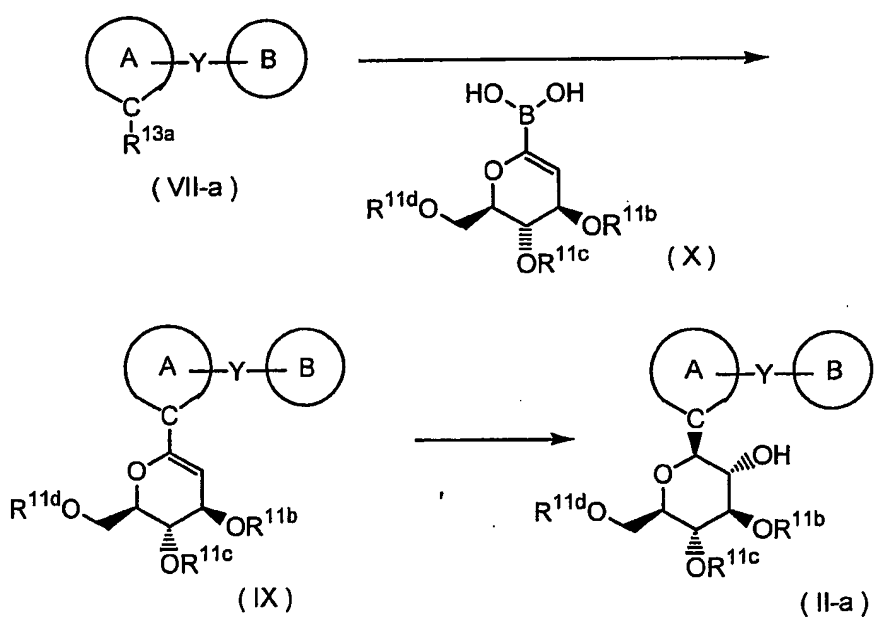
The Lewis acid includes, for example, trimethylsilyl trifluoromethanesulfonate, titanium tetrachloride, tin tetrachloride, boron trifluoride · diethyl ether complex.

The solvent may be, for example, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, etc., acetonitrile, etc.

This reaction can be carried out under cooling or with heating, for example, at a temperature of from 0°C to 100°C, preferably at a temperature of from room temperature to 60°C.

Step (c):

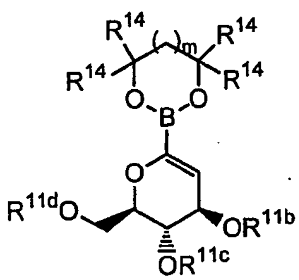
Among the compounds of the formula II, the compound wherein X is a carbon atom and R^{11a} is a hydrogen atom may be prepared by a method as shown in the following scheme:



wherein R^{13a} is a bromine atom or an iodine atom, and the other symbols are as defined above.

Namely, the compounds of the formula II-a may be prepared by coupling the compound of the formula VII-a with the compound of the formula X or an ester thereof to give the compound of the formula IX, followed by hydrating the compound of the formula IX.

The ester of the compound of the formula X includes, for example, a lower alkyl ester thereof, and a compound represented by the formula XI:



(XI)

wherein R^{14} is a lower alkyl group, m is 0 or 1, and the other symbols are as defined above.

The coupling reaction of the compound of the formula VII-a with the compound of the formula X or an ester thereof can be carried out in the presence of a base and a palladium catalyst in a suitable solvent.

The base includes an inorganic base such as an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), potassium fluoride, potassium phosphate, etc., and an organic base such as a tri-lower alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), a cyclic tertiary amine (e.g., 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[4.3.0]-nona-5-ene, 1,8-diazabicyclo[5.4.0]undeca-7-ene, etc.).

The palladium catalyst may be a conventional catalyst

such as tetrakis(triphenyl)phosphinepalladium(0), palladium(II) acetate, palladium(II) chloride, bis(triphenyl)phosphine palladium(II) chloride, palladium(II) chloride · 1,1-bis(diphenylphosphino)ferrocene complex, etc.

The solvent may be any inert solvent which does not disturb the reaction, for example, ethers such as tetrahydrofuran, dioxane, etc., amide solvents such as N,N-dimethylformamide, 1,3-dimethyl-2-imidazolidinone, etc., aromatic hydrocarbons such as toluene, xylene, etc., dimethylsulfoxide, water, and if desired, a mixture of two or more of these solvents.

This reaction is preferably carried out with heating, for example, at a temperature of from 50°C to a boiling point of the reaction mixture, and more preferably at a temperature of from 50°C to 100°C.

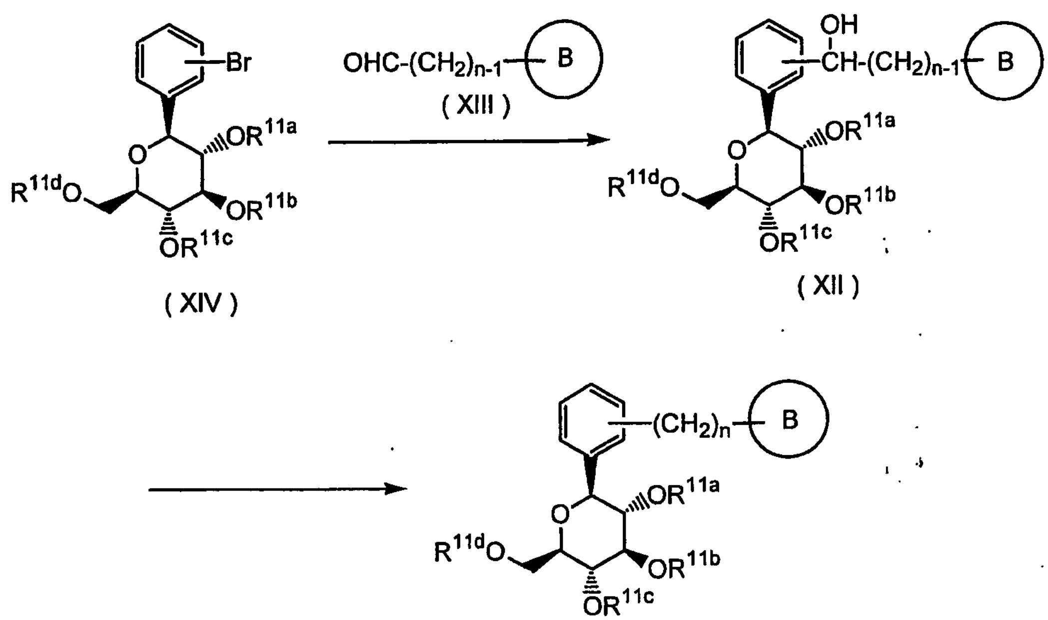
The hydration reaction of the compound of the formula IX can be carried out, for example, by hydroboration, more specifically, by reacting with diborane, borane · tetrahydrofuran complex, or 9-borabicyclononane, etc. in a suitable solvent, followed by treating with hydrogen peroxide solution in the presence of a base (e.g., an alkali metal hydroxide such as sodium hydroxide, etc.), or by treating with an oxidizing reagent such as sodium perborate, and oxodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide) in a suitable solvent.

The solvent may be any inert solvent which does not disturb the reaction, for example, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc., aromatic hydrocarbons such as benzene, toluene, xylene, etc., water, and if desired, a mixture of two or more of these solvents. This reaction can be carried out at a temperature of a broad range such as under cooling or with heating, and preferably carried out at a temperature of from

-10°C to a boiling point of the reaction mixture.

Step (d):

Among the compound of the formula II, the compound wherein Ring A is a benzene ring may be prepared in a method as shown in the following scheme:



wherein the symbols are as defined above.

Namely, the compounds of the formula II-b may be prepared by coupling the compound of the formula XIV with the compound of the formula XIII, to give the compound of the formula XII, followed by reduction of the compound of the formula XII.

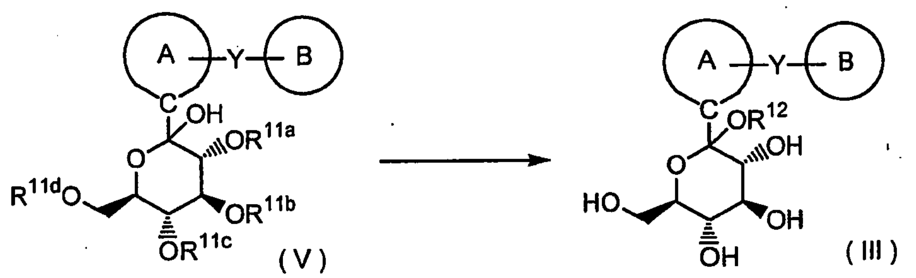
The coupling reaction can be carried out in a manner similar to Step (a). Namely, it can be carried out by lithiating the compound of formula XIV with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound (XIII).

The reduction reaction can be carried out by (1) treatment with a silane reagent (e.g., trialkyl silane such as triethyl silane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), at -30°C to 60°C, in the presence of

a Lewis acid such as boron trifluoride · diethyl ether complex or trifluoroacetic acid, (2) treatment with iodotrimethylsilane, or (3) treatment with a reducing agent (e.g., borohydrides such as sodium boron hydride, sodium triacetoxyborohydride, etc., aluminum hydrides such as lithium aluminum hydride, etc.) in the presence of an acid (e.g., a strong acid such as trifluoroacetic acid, etc., and a Lewis acid such as aluminum chloride, etc.).

Step (e):

The compound of the formula III may be prepared by a method as shown in the following scheme:



wherein the symbols are as defined above.

Namely, the compound of the formula III may be prepared by deprotecting the compound of the formula V which is a synthetic intermediate of Step (a), followed by treating the resultant compound with an acid in an alcohol solvent.

The deprotection reaction can be carried out in a manner similar to Process 1. Namely, it can be carried out by subjecting the compound V to an acid treatment, reduction, or a fluoride treatment, etc.

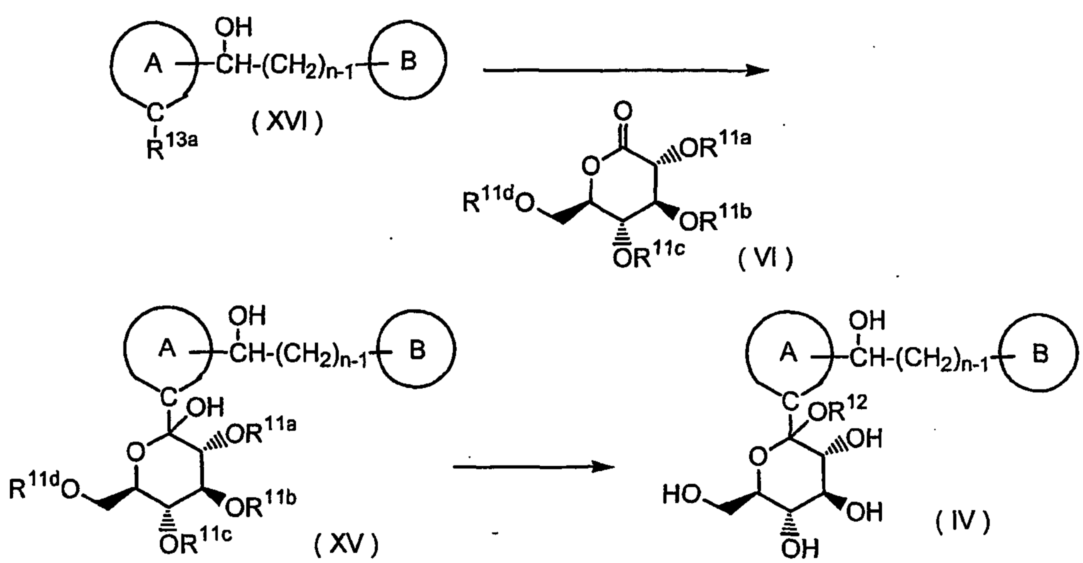
Following the deprotection reaction, the resultant compound is treated with an acid in a suitable alcohol. The acid includes, for example, an inorganic acid such as hydrochloric acid, nitric acid, sulfuric acid, etc., an organic acid such as p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc. The alcohol includes a conventional alkyl alcohol which does not disturb the reaction,

for example, methanol, ethanol, n-propanol, i-propanol, n-butanol, etc.

Additionally, the deprotection reaction and acid treatment may be carried out in the same step, depending on the kind of the protecting group.

Step (f):

The compound of the formula IV may be prepared by a method as shown in the following scheme:



wherein the symbols are as defined as above.

First, the compound of the formula XVI is coupled with the compound of the formula VI to give the compound of the formula XV. Then, after protecting groups are removed from the compound of the formula XV, the resultant is treated with an acid in an alcohol to give the compound of the formula IV.

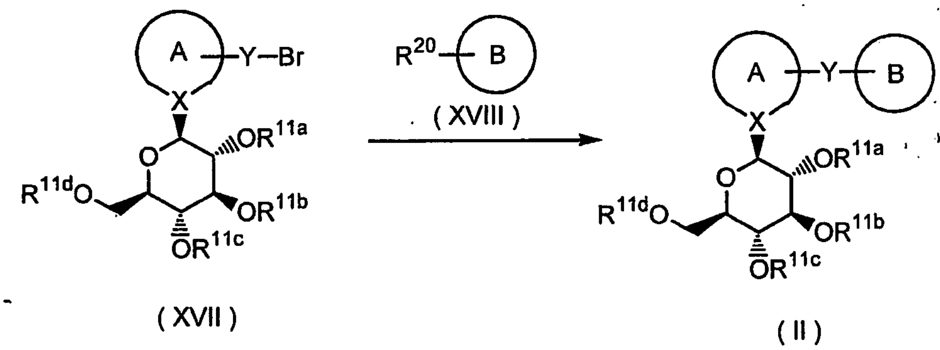
The coupling reaction can be carried out in a manner similar to Step (a). Namely, the compound XVI is treated with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc,) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound VI.

The removal of protecting groups and the acid treatment

are carried out in a manner similar to Step (e). Namely, it can be carried out by subjecting the compound XV to reduction, acid treatment or fluoride treatment, depending on the kind of the protecting group to be removed, followed by treating the resultant with an acid (e.g., hydrochloric acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc.) in a suitable solvent (e.g., methanol, ethanol, etc.).

Step (g):

The compound of the formula II may be prepared by a method as shown in the following scheme:



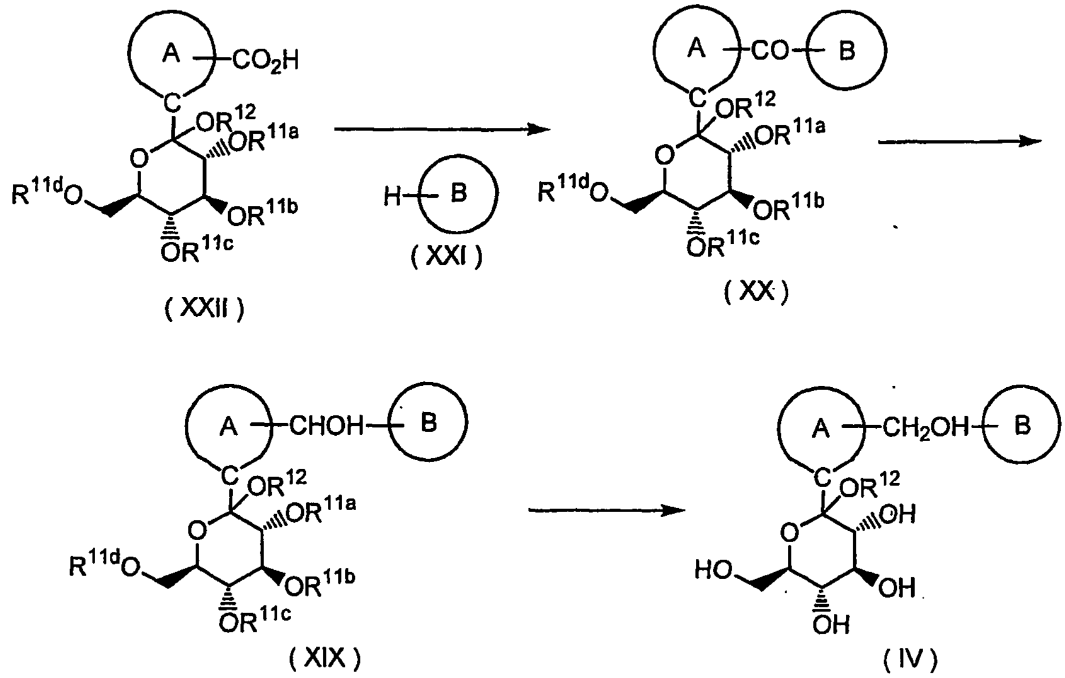
wherein R^{20} is a trialkylstannyl group, or a dihydroxyboryl group or an ester thereof, and the other symbols are as defined above.

Namely, the compound of the formula II may be prepared by coupling the compound XVII with the compound XVIII in a suitable solvent, in the presence of a palladium catalyst, and in the presence or in the absence of a base.

The coupling reaction can be carried out in a manner similar to Step (c).

Step (h):

Among the compound of the formula IV, the compound wherein n is 1 may be prepared in a method as shown in the following scheme:



wherein the symbols are as defined above.

Namely, the compound of the formula IV may be prepared by the following steps: (1) treating the compound of the formula XXII with a halogenating agent in a suitable solvent or in the absence of a solvent, followed by condensation of the resultant with the compound of the formula XXI in the presence of a Lewis acid to give the compound of formula XX, (2) reducing the compound of formula XX, and (3) removing the protecting groups from the compound of formula XIX.

The halogenating agent includes a conventional halogenating agent such as thionyl chloride, phosphorus oxychloride, oxalyl chloride, etc.

The solvent may be any solvent which does not disturb the reaction, and for example, dichloromethane, carbon tetrachloride, tetrahydrofuran, toluene, etc. may be mentioned.

Further, in the present reaction, the reaction suitably proceeds by adding a catalyst such as dimethylformamide, etc.

The condensation reaction of the compound (XXII) and the compound (XXI) can be carried out according to a conventional

method as known as Friedel-Crafts reaction, in the presence of a Lewis acid and in a suitable solvent.

The Lewis acid includes aluminum chloride, boron trifluoride · diethyl ether complex, tin(IV) chloride, titanium tetrachloride, etc. which are conventionally used in Friedel-Crafts reaction.

The solvent includes halogenated hydrocarbons such as dichloromethane, carbon tetrachloride, dichloroethane, etc.

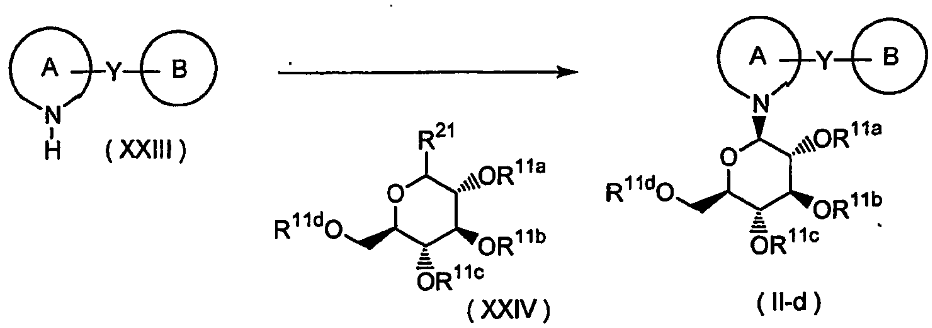
The reduction reaction can be carried out by treating the compound of formula XX with a silane reagent (e.g., trialkyl silane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., a Lewis acid such as boron trifluoride · diethyl ether complex, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc.), or by treating with a hydrazine in a suitable solvent (e.g., ethylene glycol, etc.) in the presence of a base (e.g., potassium hydroxide, etc.).

The present reaction can be carried out under cooling or with heating, for example, at a temperature of from -30°C to 60°C.

The removal of the protecting groups from the compound of formula XIX can be carried our in a manner similar to Process 1.

Step (i):

Among the compounds of the formula II, the compound wherein X is a nitrogen atom may be prepared by a method as shown in the following scheme:



wherein R^{21} is a leaving group, and the other symbols are as defined above.

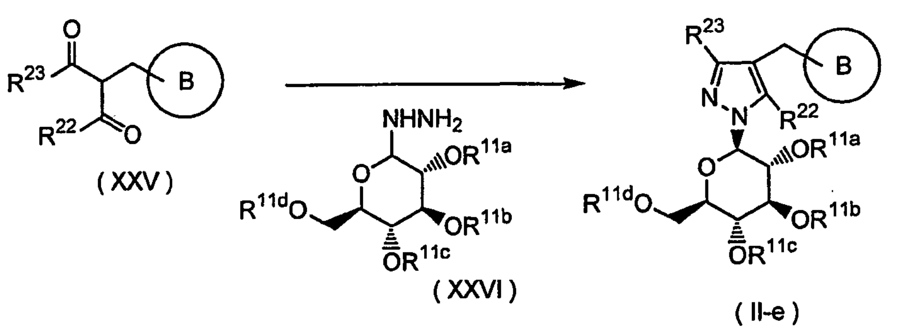
Examples of the leaving group include a halogen atom such as chlorine atom and bromine atom.

Namely, the compound of the formula II-d may be prepared by condensation of the compound of the formula XXIII with the compound of the formula XXIV.

The condensation reaction can be carried out in a suitable solvent such as acetonitrile, etc., in the presence of a base (e.g., an alkali metal hydroxide, such as potassium hydroxide, etc.).

Step (j):

Among the compound of the formula II, the compound wherein Ring A is a pyrazole substituted by a lower alkyl group, X is a nitrogen atom and Y is $-CH_2-$ may be prepared by a method as shown in the following scheme:



wherein R^{22} and R^{23} are each independently a lower alkyl group, and the other symbols are as defined above.

Namely, the compound II-e may be prepared by condensation

of the compound of the formula XXV with the compound of the formula XXVI in a suitable solvent (e.g., ethers such as tetrahydrofuran, etc., an aromatic hydrocarbons such as toluene, etc.).

Further, the compound of the present invention may be converted to each other within the objective compounds of the present invention. Such conversion reaction may be carried out according to a conventional method, depending on the kind of the objective substituents.

For example, a compound having as a substituent of Ring B, an aryl group such as phenyl group, or a heterocyclyl group may be prepared by coupling the compound in which substituents of the Ring B is a halogen atom such as a bromine atom, with a suitable phenylboronic acid, phenyltin, hetercyclylboronic acid, or heterocyclyltin.

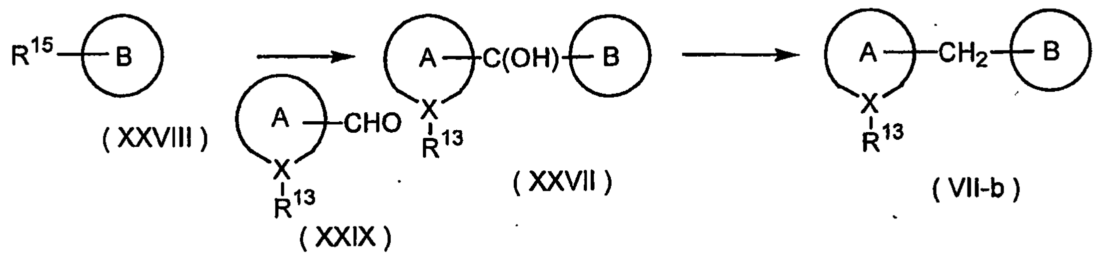
The coupling reaction may be carried out in a manner similar to Step (c) or Step (g), or in a method as described in the following Examples.

In the present compound, the compound wherein heteroatom is oxidized (e.g., S-oxide, S,S-oxide, or N-oxide compounds) may be prepared by oxidizing a corresponding S-form or N-form.

The oxidation reaction can be carried out by a conventional method, for example, by treatment with an oxidizing agent (e.g., peracids such as hydrogen peroxide, m-chloroperbenzoic acid, peracetic acid, etc.) in a suitable solvent (e.g., halogenated hydrocarbons such as dichloromethane, etc.).

The starting compounds of the respective steps described above may be prepared by the methods as disclosed in Reference Examples or a process as mentioned below.

(1) Among the compounds of the formula VII, the compound wherein Y is $-CH_2-$ may be prepared by a method as shown in the following scheme:



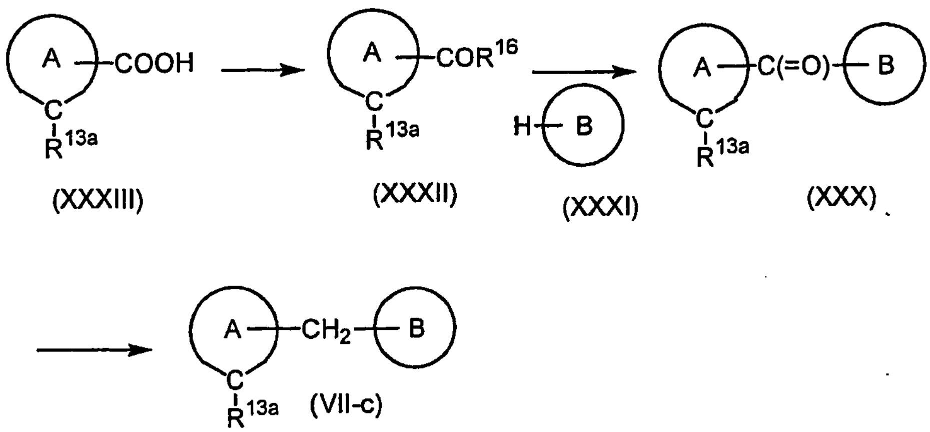
wherein R^{15} is a hydrogen atom or a halogen atom, and the other symbols are as defined above.

Namely, the compound of the formula VII-b may be prepared by coupling the compound of the formula XXVIII with the compound of the formula XXIX to give the compound of the formula XXVII, followed by reducing the obtained compound of the formula XXVII.

The coupling reaction of the present step may be carried out in a manner similar to Step (a). Namely, the compound of the formula XXVIII is treated with an alkyl lithium (e.g., n-butyl lithium, tert-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), followed by reacting the resultant with the compound of the formula XXIX.

The reduction reaction may be carried out in a manner similar to Step (d), more specifically, by (1) treatment with a silane reagent such as triethylsilane, etc., in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), at -30°C to 60°C, in the presence of a Lewis acid such as boron trifluoride · diethyl ether complex or trifluoroacetic acid, (2) treatment with iodotrimethylsilane , or (3) treatment with a reducing agent (e.g., borohydrides such as sodium boron hydride, sodium triacetoxyborohydride, etc., aluminum hydrides such as lithium aluminum hydride, etc.) in the presence of an acid (e.g., a strong acid such as trifluoroacetic acid, etc., a Lewis acid such as aluminum chloride, etc.).

(2) Among the compound of the formula VII, the compound wherein X is a carbon atom and Y is $-CH_2-$ may be prepared by a method as shown in the following scheme:



wherein R^{16} is a halogen atom, and the other symbols are as defined above.

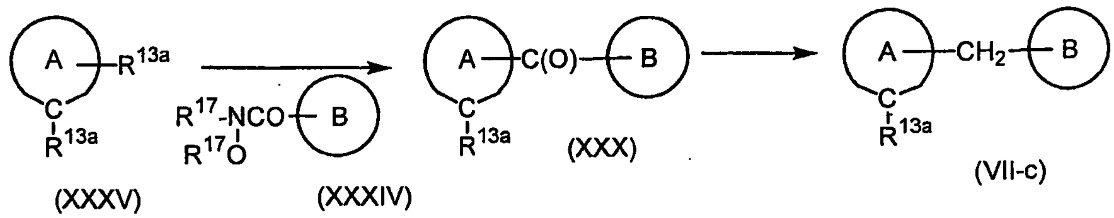
The present process may be carried out in a manner similar to Step (h) as mentioned above.

Namely, the compound of the formula VII-c may be prepared by treating the compound of the formula XXXIII with a halogenating reagent (e.g., thionyl chloride, phosphorus oxychloride, oxalyl chloride, etc.) in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, tetrahydrofuran, toluene, etc.) or in the absence of a solvent, to give the compound of the formula XXXII, subsequently by condensing this compound with the compound of the formula XXXI in a suitable solvent (e.g., dichloromethane, carbon tetrachloride, dichloroethane, etc.) in the presence of a Lewis acid (e.g., aluminum chloride, zinc chloride, titanium tetrachloride, etc.), to give the compound of the formula XXX, and further by reducing the obtained compound.

The reduction reaction can be carried out by treating with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., a Lewis acid such as boron trifluoride · diethyl ether complex, etc., and a strong organic acid such as trifluoroacetic acid, methanesulfonic acid, etc.), or by treating with a hydrazine in a suitable solvent (e.g., ethylene

glycol, etc.) in the presence of a base (e.g., potassium hydroxide, etc.).

(3) Among the compounds of the formula VII, the compound wherein X is a carbon atom and Y is $-CH_2-$ may be prepared by a method as shown in the following scheme:



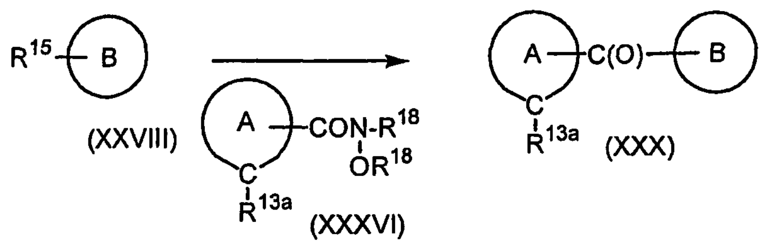
wherein R^{17} is a lower alkyl group, and the other symbols are as defined above.

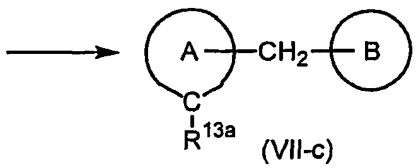
The compound of the formula VII-c may be prepared by coupling the compound of the formula XXXV with the compound of the formula XXXIV to give the compound of the formula XXX, and subsequently by reducing the obtained compound .

The coupling reaction may be carried out in a manner similar to Step (a). Namely, the compound of the formula (XXV) is lithiated with an alkyllithium (e.g., tert-butyl lithium, n-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), and subsequently, by reacting the resultant with the compound (XXIV).

The reduction reaction may be carried out in a manner similar to Step (a). Namely, it can be carried out by treating the compound of formula XXX with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.), in the presence of an acid (e.g., boron trifluoride · diethyl ether complex, etc).

(4) Among the compound of the formula VII, the compound wherein X is a carbon atom and Y is $-CH_2-$ may be prepared by a method as shown in the following scheme:





wherein R^{18} is a lower alkyl group, and the other symbols are as defined above.

Namely, the compound of the formula VII-c may be prepared by coupling the compound of the formula XXVIII with the compound of the formula XXXVI to give the compound of the formula XXX, and subsequently by reducing the compound.

The present process may be carried out in a manner similar to Step (3). Namely, the compound of the formula (XXVIII) is lithiated with an alkyllithium (e.g., tert-butyl lithium, n-butyl lithium, etc.) in a suitable solvent (e.g., diethyl ether, tetrahydrofuran, etc.), and subsequently, by reacting the resultant with the compound (XXXVI) to give the compound of the formula (XXX). Subsequently, the compound of the formula XXX is treated with a silane reagent (e.g., triethylsilane, etc.) in a suitable solvent (e.g., acetonitrile, dichloromethane, etc.) in the presence of an acid (e.g., boron trifluoride · diethyl ether complex, etc), to give the compound of the formula (VII-c).

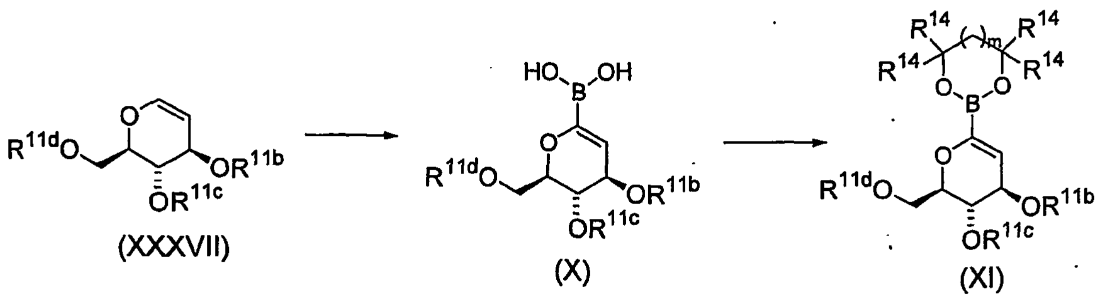
The compound of the formula XIV wherein Ring A is a benzene ring is disclosed in WO 01/27128 pamphlet.

The compound of the formula VI is disclosed in WO 01/27128 or Benhaddu, S. Czernecki et al., Carbohydr. Res., vol. 260, p. 243-250, 1994.

The compound of the formula VIII may be prepared from

D-(+)-glucono-1,5-lactone according to the method disclosed in USP 6515117.

The compound of the formula X and the compound of the formula XI may be prepared by the following Reaction Scheme:



wherein the symbols are as defined above.

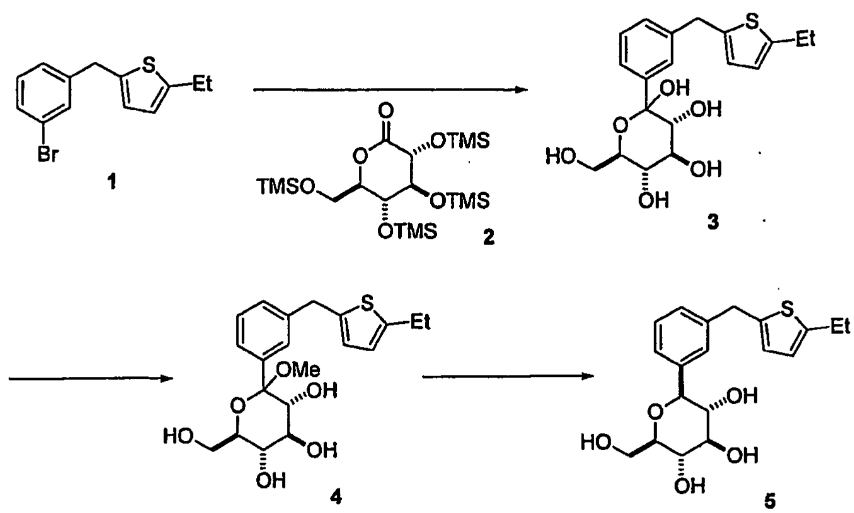
First, the compound of the formula XXXVII is lithiated with t-butyl lithium in a suitable solvent (e.g., tetrahydrofuran, etc.) under cooling (e.g., -78°C), followed by reacting with trimethyl borate to give the compound of the formula X.

Then, the compound of the formula X is reacted with a 1,2-diol (e.g., pinacol, etc.) or 1,3-diol (e.g., 2,4-dimethyl-2,4-pentanediol, etc.) to give the compound of the formula XI.

The other starting compounds are commercially available or may easily be prepared by a standard method well known to an ordinary skilled person in this field.

Hereinafter, the present invention will be illustrated by Examples and Reference Examples, but the present invention should not be construed to be limited thereto.

<u>Example 1 1-(β-D-glucopyranosyl)-3-(5-ethyl-2-thienyl-methyl)benzene</u>

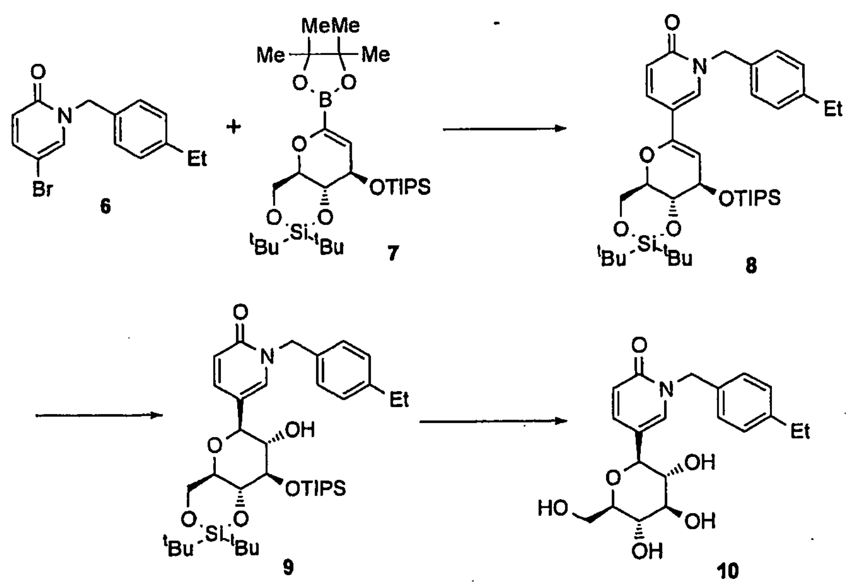


In the above scheme, Me is a methyl group, Et is an ethyl group, TMSO and OTMS are a trimethylsilyloxy group.

(1) 3-Bromo-(5-ethyl-2-thienylmethyl)benzene 1 (211 mg) was dissolved in tetrahydrofuran (2 ml) - toluene (4 ml), and the mixture was cooled to -78°C under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.44 M hexane solution, 0.29 ml), and the mixture was stirred at the same temperature for 30 minutes. Then, a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see USP 6,515,117) (233 mg) in toluene (5 ml) was added dropwise, and the mixture was further stirred at the same temperature for one hour to give a lactol compound 3. Without isolating this compound, a solution of methanesulfonic acid (0.1 ml) in methanol (5 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol = 19:1) to give a methyl ether compound 4 (136 mg) of the lactol. APCI-Mass m/Z 412 $(M+NH_4)$.

(2) A solution of the above methyl ether compound 4 (100 mg) in dichloromethane (5 ml) was cooled to -78°C under argon atmosphere, and thereto were added dropwise successively triisopropylsilane (0.16 ml), and boron trifluoride · diethyl ether complex (0.10 ml). The mixture was stirred at the same temperature for 10 minutes, and warmed. The mixture was stirred at 0°C for 1 hour and 20 minutes, and then further stirred at room temperature for 2 hours. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform: methanol = 19:1) to give the desired 1-(β-D-glucopyranosyl)-3-(5-ethyl-2-thienylmethyl)benzene 5 (59 mg). APCI-Mass m/Z 382 ($M+NH_4$).

Example 2 5-(β-D-glucopyranosyl)-1-(4-ethylphenyl-methyl)-1H-pyridin-2-one



In the above scheme, tBu is a tert-butyl group, OTIPS is a triisopropylsilyloxy group, and the other symbols are as defined above.

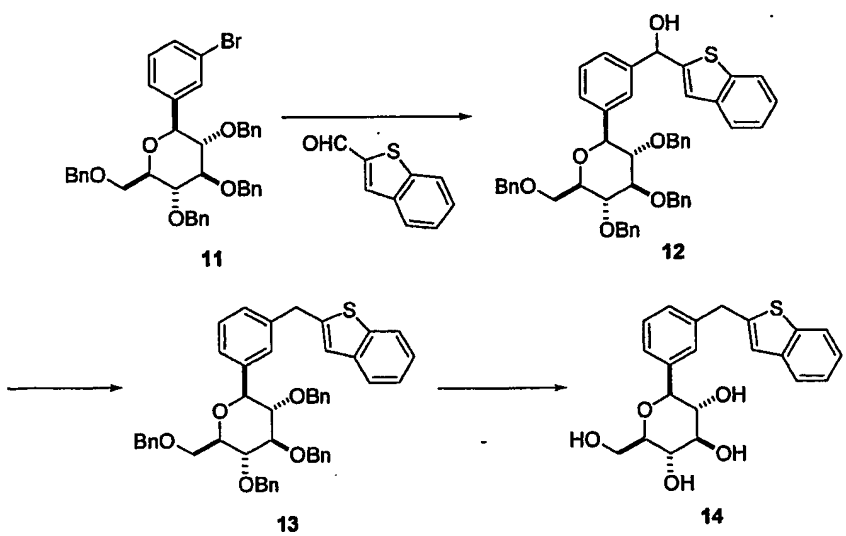
(1) 5-Bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one 6 (293 mg) and boronic acid ester of glucal 7 (1.0 g) were dissolved in dimethoxyethane (5 ml). To the mixture were added bis(triphenyl)phosphine palladium(II) dichloride (35 mg) and 2M sodium carbonate (2.5 ml), and the mixture was heated with stirring under reflux under argon atmosphere for 5 hours. The mixture was cooled to room temperature, and the reaction solution was diluted with ethyl acetate, and washed with water. The organic layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 95:5 - 70:30) to give glucal derivative 8 (276 mg) as colorless powder. APCI-Mass m/Z 654 (M+H).

(2) A solution of glucal derivative 8 (260 mg) in tetrahydrofuran (5 ml) was cooled to 0°C under argon atmosphere, and thereto was added dropwise a solution of borane · tetrahydrofuran complex (1.13 M tetrahydrofuran solution, 1.06 ml), and the reaction solution was stirred at the same temperature overnight. A mixture of an aqueous hydrogen peroxide solution (31 %, 5.0 ml) and 3N aqueous sodium hydroxide solution (5.0 ml) was added to the reaction solution, and the mixture was warmed to room temperature, and stirred for 30 minutes. To the mixture was added 20 % aqueous sodium thiosulfate solution (30 ml), and the mixture was extracted with ether. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 96:4 - 66.34) to give C-glucoside compound 9 (59 mg) as colorless powder. APCI-Mass m/Z 672 (M+H).

(3) The above C-glucoside compound 9 (55 mg) was dissolved in tetrahydrofuran (2 ml), and thereto was added tetrabutyl ammonium fluoride (1.0 M tetrahydrofuran solution, 0.41 ml).

The mixture was heated with stirring under reflux for 3 hours under argon atmosphere, and the reaction solution was cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 - 88:12) to give the desired 5-(β-D-glucopyranosyl)-1-(4-ethylphenylmethyl)-1H-pyridin-2-one 10 (10 mg) as colorless powder. APCI-Mass m/Z 376 (M+H).

Example 3 1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-2-ylmethyl)benzene



In the above scheme, Bn is a benzyl group.

(1) β-m-Bromophenyl-tetra-O-benzyl-C-glucoside 11 (see WO 01/27128)(1.00 g) was dissolved in diethyl ether (60 ml), and the mixture was cooled to -78°C under argon atmosphere. To the mixture was added dropwise t-butyl lithium (1.49 M pentane solution, 0.99 ml), and the mixture was stirred at the same temperature for 10 minutes. Then, a solution of 2-formylbenzo[b]thiophene (286 mg) in diethyl ether (2 ml) was added dropwise, and the mixture was further stirred at the same temperature for 30 minutes. To the reaction mixture was added a saturated aqueous ammonium chloride solution, and the mixture

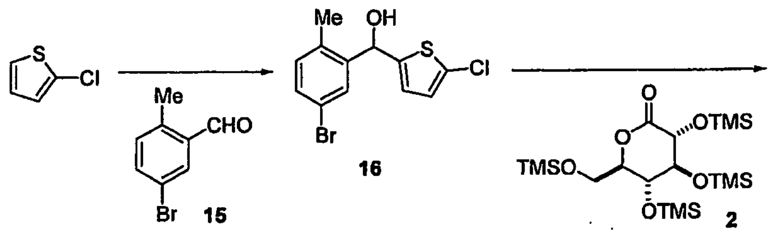
was warmed to room temperature. The mixture was extracted with diethyl ether, the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 90:10-50:50) to give an alcohol compound 12 (835 mg). APCI-Mass m/Z 780 ($M+NH_4$).

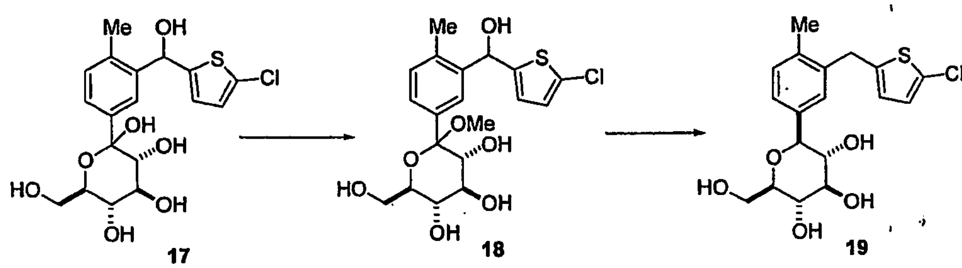
(2) A solution of the above alcohol compound 12 (820 mg) in dichloromethane (15 ml) was cooled to -78°C under argon atmosphere, and thereto were added dropwise successively triethylsilane (0.52 ml), and boron trifluoride · diethyl ether complex (0.20 ml). The reaction mixture was warmed to room temperature and stirred at the same temperature for 30 minutes. Added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with dichloromethane. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 94:6-75:25) to give the compound 13 (703 mg). APCI-Mass m/Z 764 ($M+NH_4$).

(3) A solution of the above compound 13 (690 mg) in dichloromethane (20 ml) was cooled to 0°C, and iodotrimethylsilane (0.66 ml) was added thereto and the mixture was stirred at room temperature for one hour. Addition of iodotrimethylsilane and stirring at room temperature were repeated in the same manner for 3 times. Total amount of the iodotrimethylsilane was summed up to 2.64 ml. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted with diethyl ether twice, and washed with an aqueous sodium thiosulfate solution. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 - 89:11) to give the desired 1-(β-D-glucopyranosyl)-3-(benzo[b]thiophen-

2-ylmethyl)benzene 14 (180 mg). APCI-Mass m/Z 404 ($M+NH_4$).

Example 4 1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene





In the above scheme, the symbols are as defined above.

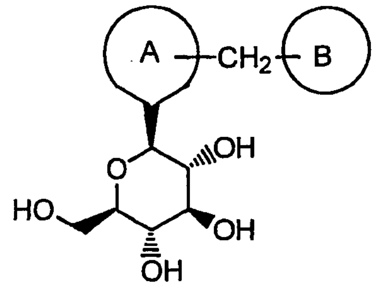
(1) A solution of 2-chlorothiophene (447 mg) in tetrahydrofuran (10 ml) was cooled to -78°C under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 2.61 ml). The mixture was stirred at the same temperature for one hour, and added dropwise thereto was a solution of 5-bromo-2-methylbenzaldehyde 15 (750 mg) in tetrahydrofuran (5 ml). The mixture was stirred at the same temperature for 30 minutes to give a compound 16. Toluene (30 ml) was added, and further added dropwise thereto was n-butyl lithium (1.59 M hexane solution, 2.37 ml). The mixture was further stirred at the same temperature for 30 minutes, and a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see USP 6,515,117) (1.76 g) in toluene (5 ml) was added dropwise, and the mixture was further stirred at the same temperature for one and a half hours to give a lactol compound 17. Subsequently, a solution of methanesulfonic acid (1.22 ml) in methanol (25 ml) was added to the reaction solution,

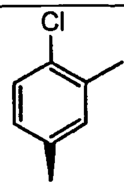
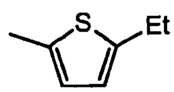
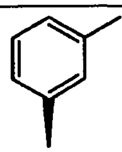
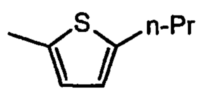
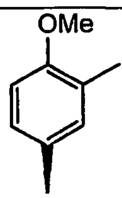
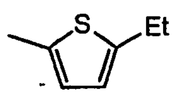
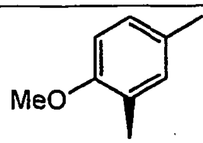
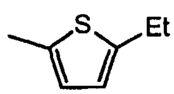
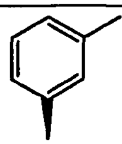
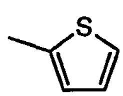
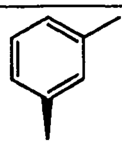
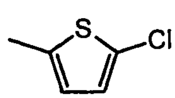
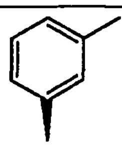
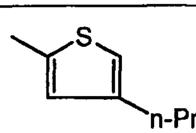
and the mixture was stirred at room temperature overnight. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give a crude methyl ether compound 18, which was used in the subsequent step without further purification.

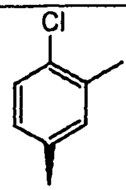
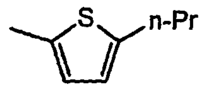
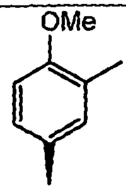
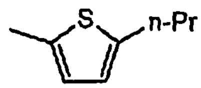
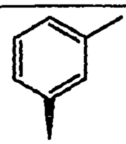
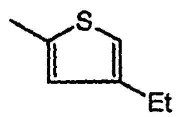
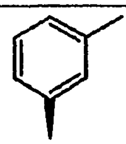
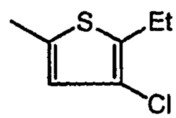
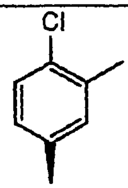
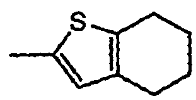
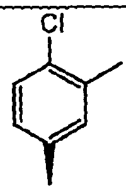
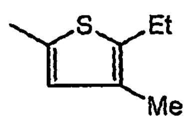
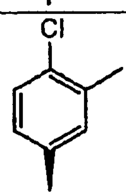
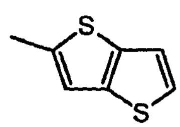
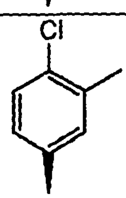
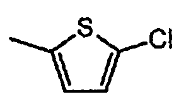
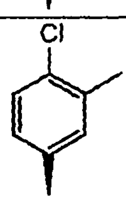
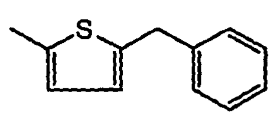
(2) A solution of the above crude methyl ether compound 18 in dichloromethane (25 ml) was cooled to -78°C under argon atmosphere, and thereto were added dropwise successively triethylsilane (3.01 ml), and boron trifluoride · diethyl ether complex (2.39 ml). The reaction mixture was warmed to 0°C, and stirred at the same temperature for 3 hours. Added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform: methanol = 100:0-92:8) to give the desired 1-(β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 19 (183 mg). APCI-Mass m/Z 402/404 ($M+NH_4$).

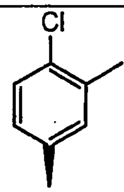
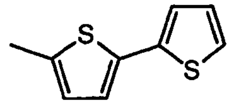
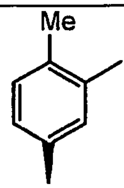
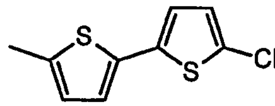
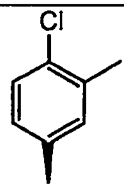
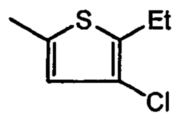
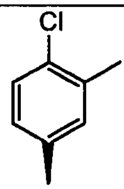
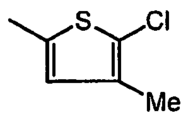
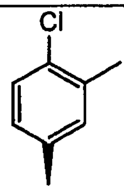
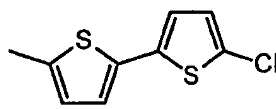
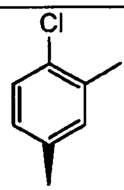
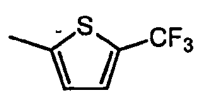
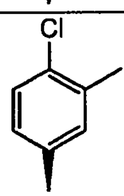
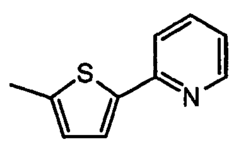
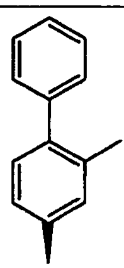
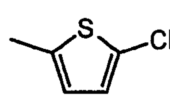
In a manner similar to the method disclosed in any of the above Examples 1 to 4, the compounds shown in Table 1 below were prepared from corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out.

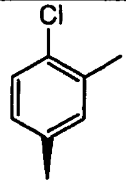
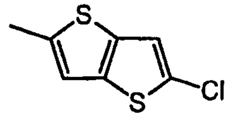
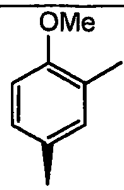
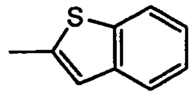
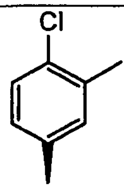
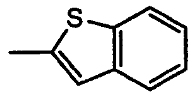
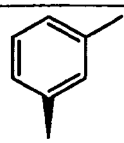
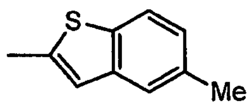
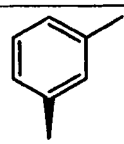
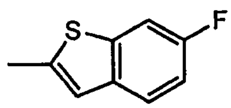
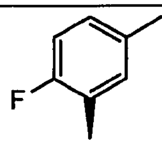
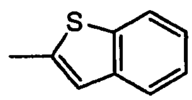
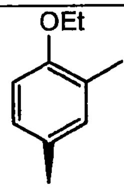
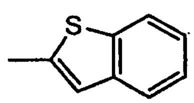
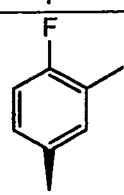
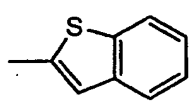
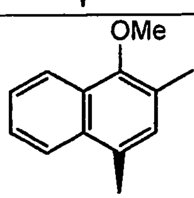
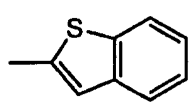
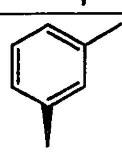
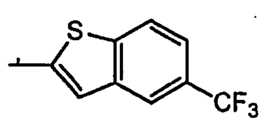
Table 1

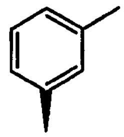
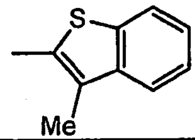
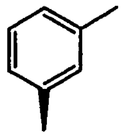
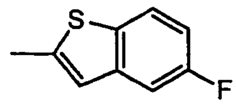
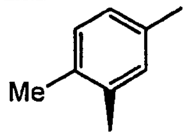
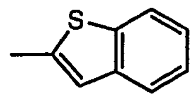
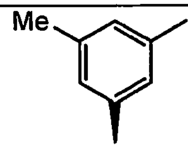
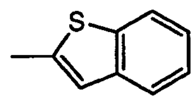
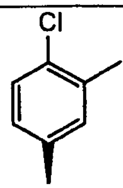
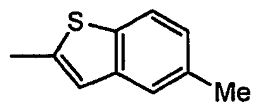
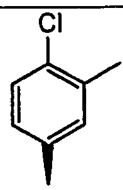
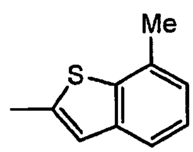
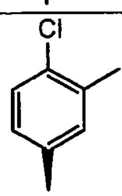
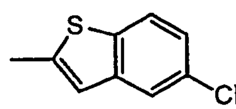
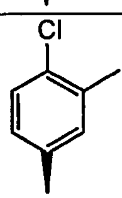
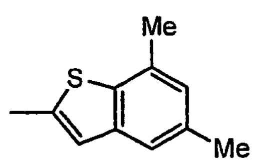
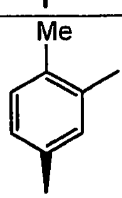
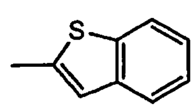
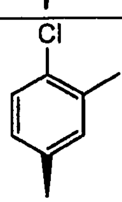
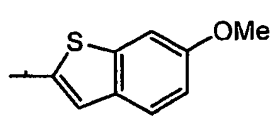


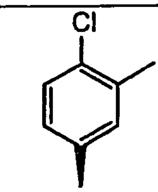
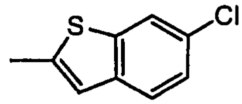
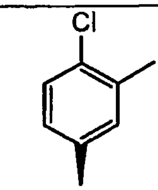
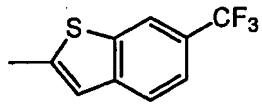
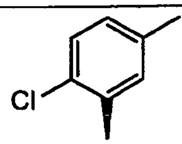
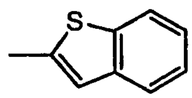
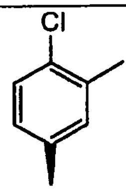
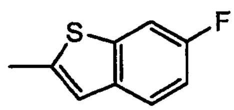
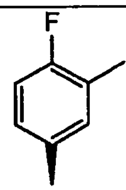
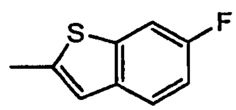
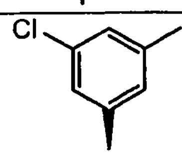
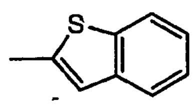
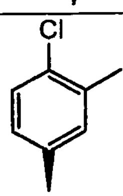
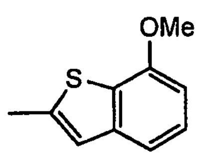
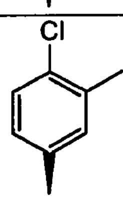
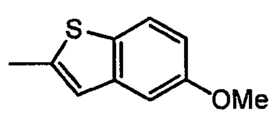
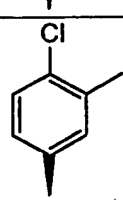
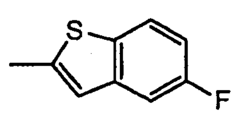
Examples	Ring A	Ring B	Preparation Method	APCI-Mass (m/Z)
5			1	416/418 (M+NH4)
6			1	396 (M+NH4)
7			1	412 (M+NH4)
8			1	412 (M+NH4)
9			3	354 (M+NH4)
10			3	388/390 (M+NH4)
11			1	396 (M+NH4)

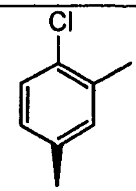
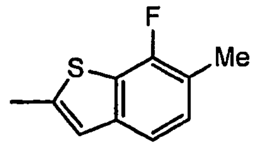
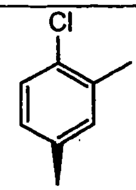
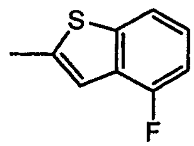
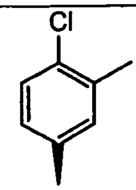
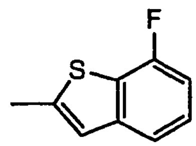
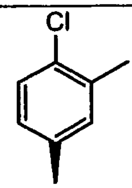
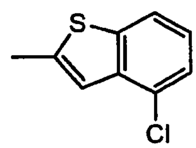
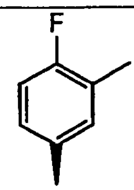
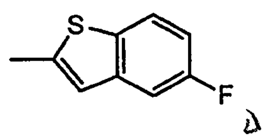
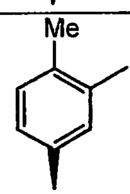
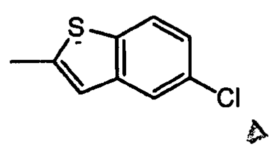
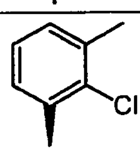
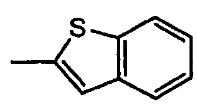
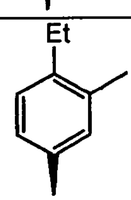
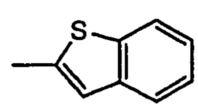
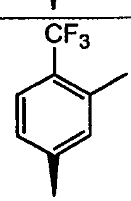
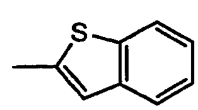
1 2			1	430/432 (M+NH_4)
1 3			1	426 (M+NH_4)
1 4			1	382 (M+NH_4)
1 5			1	416/418 (M+NH_4)
1 6			1	442/444 (M+NH_4)
1 7			1	430/432 (M+NH_4)
1 8			2	444/446 (M+NH_4)
1 9			1	422/424 (M+NH_4)
2 0			1	478/480 (M+NH_4)

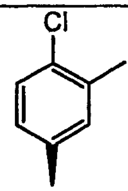
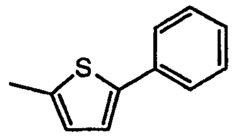
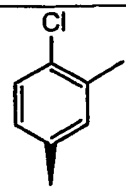
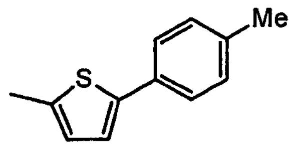
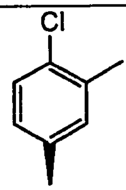
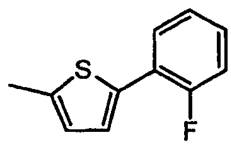
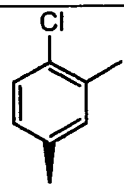
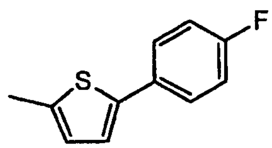
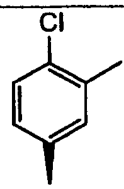
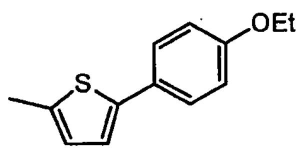
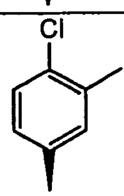
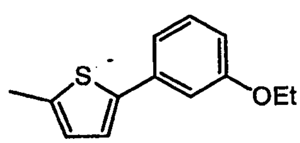
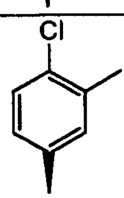
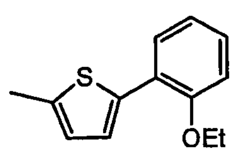
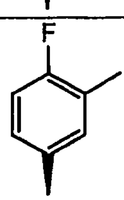
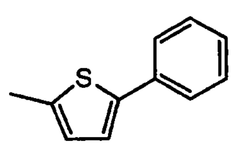
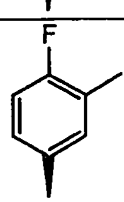
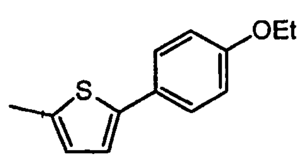
2 1			2	470/472 (M+NH4)
2 2			1	484/486 (M+NH4)
2 3			1	450/452 (M+NH4)
2 4			4	436/438 (M+NH4)
2 5			1	504/506 (M+NH4)
2 6			2	456/458 (M+NH4)
2 7			1	448/450 (M+NH4)
2 8			1	464/466 (M+NH4)

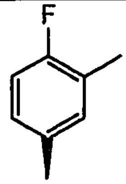
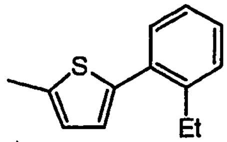
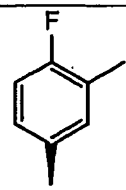
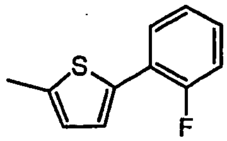
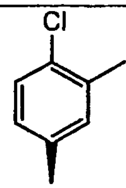
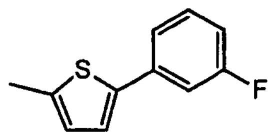
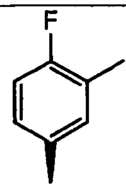
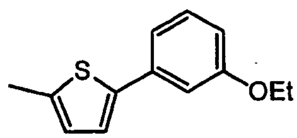
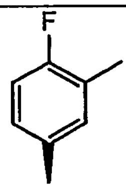
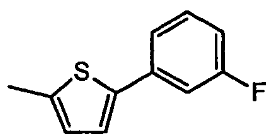
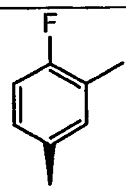
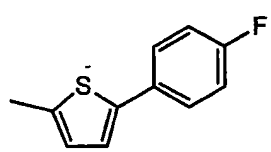
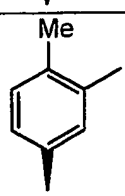
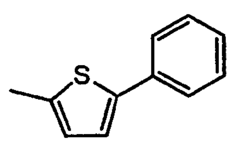
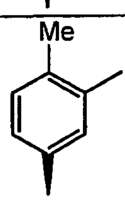
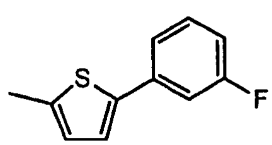
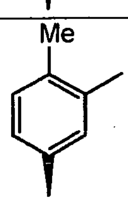
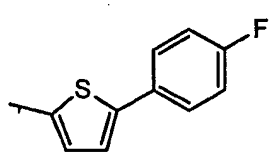
29			4	478/480 (M+NH_4)
30			1	434 (M+NH_4)
31			1	438/440 (M+NH_4)
32			1	418 (M+NH_4)
33			1	422 (M+NH_4)
34			1	422 (M+NH_4)
35			1	448 (M+NH_4)
36			1	422 (M+NH_4)
37			1	484 (M+NH_4)
38			1	472 (M+NH_4)

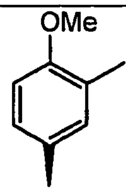
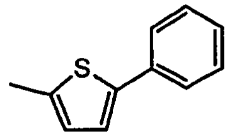
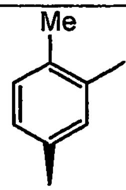
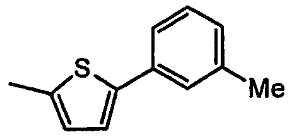
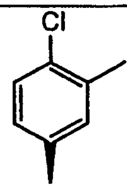
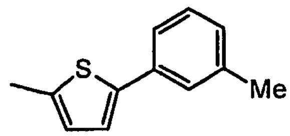
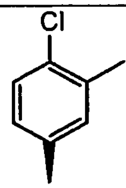
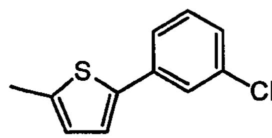
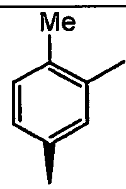
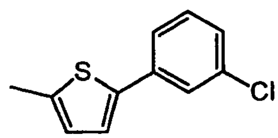
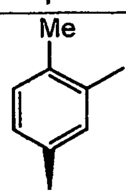
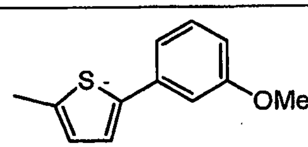
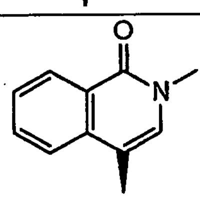
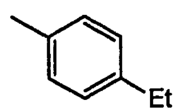
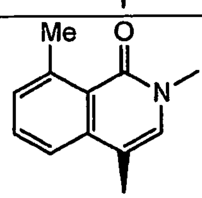
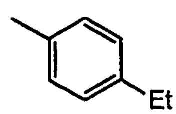
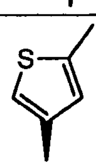
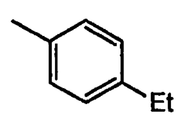
39			1	418 (M+NH4)
40			1	422 (M+NH4)
41			2	418 (M+NH4)
42			1	418 (M+NH4)
43			1	452/454 (M+NH4)
44			1	452/454 (M+NH4)
45			1	472/474 (M+NH4)
46			1	466/468 (M+NH4)
47			1	418 (M+NH4)
48			1	468/470 (M+NH4)

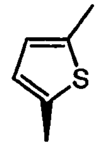
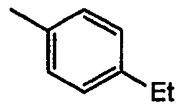
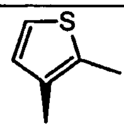
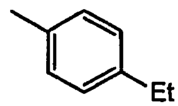
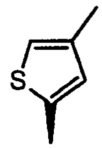
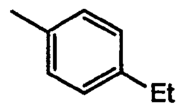
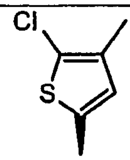
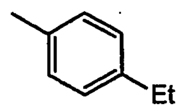
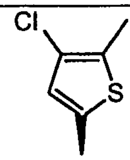
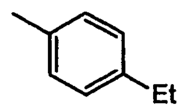
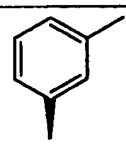
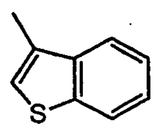
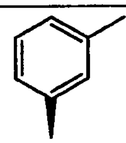
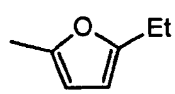
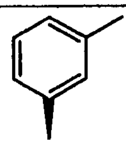
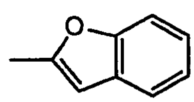
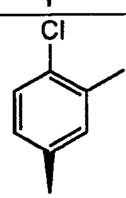
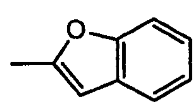
49			1	472/474 (M+NH4)
50			2	506/508 (M+NH4)
51			2	438/440 (M+NH4)
52			2	456/458 (M+NH4)
53			2	440 (M+NH4)
54			2	438/440 (M+NH4)
55			1	468/470 (M+NH4)
56			1	468/470 (M+NH4)
57			2	456/458 (M+NH4)

5 8			1	470/472 (M+NH_4)
5 9			2	456/458 (M+NH_4)
6 0			2	456/458 (M+NH_4)
6 1			2	472/474 (M+NH_4)
6 2			2	440 (M+NH_4)
6 3			4	452/454 (M+NH_4)
6 4			2	438/440 (M+NH_4)
6 5			1	432 (M+NH_4)
6 6			2	472 (M+NH_4)

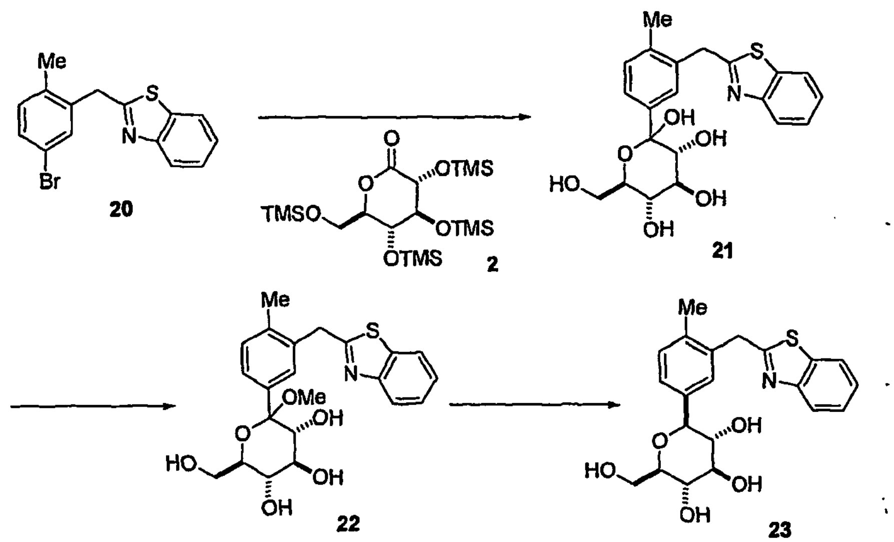
6 7			1	464/466 (M+NH4)
6 8			1	478/480 (M+NH4)
6 9			1	482/484 (M+NH4)
7 0			1	482/484 (M+NH4)
7 1			1	508/510 (M+NH4)
7 2			1	508/510 (M+NH4)
7 3			1	508/510 (M+NH4)
7 4			1	448 (M+NH4)
7 5			1	492 (M+NH4)

7 6			1	492 (M+NH_4)
7 7			1	466 (M+NH_4)
7 8			1	482/484 (M+NH_4)
7 9			1	492 (M+NH_4)
8 0			1	466 (M+NH_4)
8 1			1	466 (M+NH_4)
8 2			1	444 (M+NH_4)
8 3			1	462 (M+NH_4)
8 4			1	462 (M+NH_4)

8 5			2	460 $(M+NH_4)$
8 6			1	458 $(M+NH_4)$
8 7			1	478/480 $(M+NH_4)$
8 8			1	498/500 $(M+NH_4)$
8 9			1	478/480 $(M+NH_4)$
9 0			1	474 $(M+NH_4)$
9 1			2	426 (M+H)
9 2			2	440 (M+H)
9 3			2	382 $(M+NH_4)$

94			2	382 (M+NH4)
95			2	382 (M+NH4)
96			2	382 (M+NH4)
97			2	416/418 (M+NH4)
98			2	416/418 (M+NH4)
99			1	404 (M+NH4)
100			1	366 (M+NH4)
101			1	388 (M+NH4)
102			1	422/424 (M+NH4)

<u>Example 103 1-(β-D-glucopyranosyl)-3-(benzothiazol-2-yl-methyl)-4-methylbenzene</u>



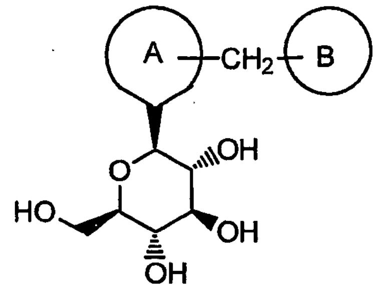
In the above scheme, the symbols are as defined above.

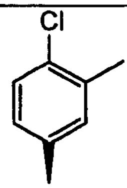
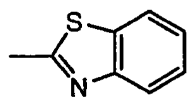
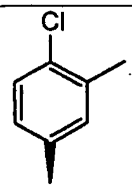
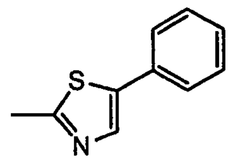
(1) 1-(benzothiazol-2-ylmethyl)-5-bromo-2-methylbenzene 20 (495 mg) was dissolved in tetrahydrofuran (5 ml) - toluene (10 ml), and the mixture was cooled to -78°C under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.44 M hexane solution, 0.67 ml), and successively was added dropwise t-butyl lithium (2.44 M pentane solution, 1.57 ml). The mixture was stirred at the same temperature for 10 minutes, and then, a solution of 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono1,5-lactone 2 (see USP 6,515,117) (2.17 g) in toluene (5 ml) was added dropwise, and the mixture was further stirred at the same temperature for 15 minutes to give a lactol compound 21. Without isolating this compound, a solution of methanesulfonic acid (1.5 ml) in methanol (25 ml) was added to the reaction solution, and the mixture was stirred at room temperature overnight. Under ice-cooling, to the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give a methyl ether compound 22, which was used in the subsequent step without further purification.

(2) A solution of the above methyl ether compound 22 in dichloromethane (20 ml)- acetonitrile (10 ml) was cooled to -78°C under argon atmosphere, and thereto were added dropwise successively triethylsilane (1.24 ml), and boron trifluoride · diethyl ether complex (0.99 ml). The mixture was warmed to room temperature and stirred at the same temperature for 30 minutes. Under ice-cooling, a saturated aqueous sodium hydrogen carbonate solution was added, and the solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol = 100:0-85:15) to give 1-(β-D-glucopyranosyl)-3-(benzothiazol-2-ylmethyl)-4-methylbenzene 23 (200 mg) as colorless powder. APCI-Mass m/Z 402 (M+H).

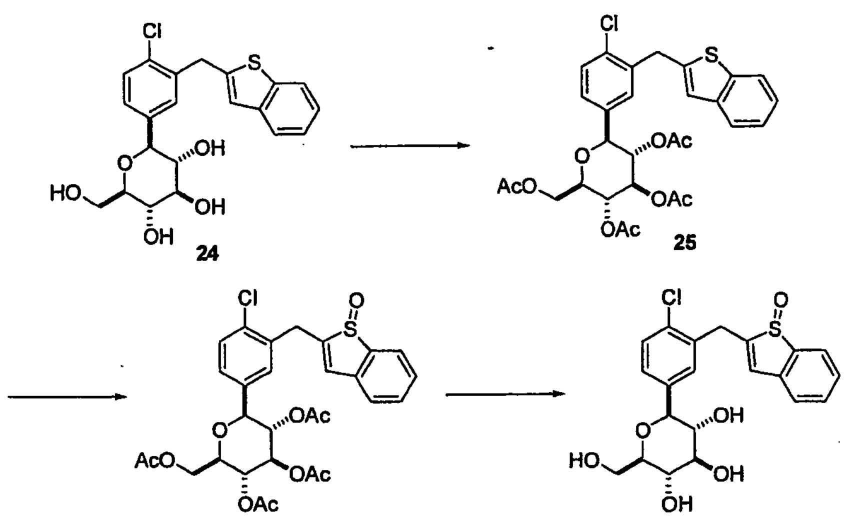
In a manner similar to Examples 103, the compounds shown in Table 2 below were prepared from corresponding starting materials.

Table 2



Examples	Ring A	Ring B	APCI-Mass (m/Z)
104			422/424 (M+H)
105			480/482 $(M+NH_4)$

Example 106 1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxy-benzo[b]thiophen-2-ylmethyl)benzene



24 25 26 27

In the above scheme, AcO and OAc are an acetyloxy group.

(1) The compound 24 (9.61 g) obtained in Example 31 was dissolved in chloroform (100 ml), and to the mixture were added acetic anhydride (21.6 ml), pyridine (18.5 ml), and

4-dimethylaminopyridine (128 mg), and the mixture was stirred at room temperature for 3.5 days. Then, Chloroform was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (200 ml). The solution was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, dried over magnesium sulfate, and treated with activated carbon. The solvent was evaporated under reduced pressure, and the residue was crystallized from ethanol to give a tetraacetate compound 25 (6.14 g). APCI-Mass m/Z 606/608 ($M+NH_4$).

(2) The above tetraacetate compound 25 (1.00 g) was dissolved in dichloromethane (20 ml), and under ice-cooling, m-chloroperbenzoic acid (439 mg) was added thereto, and the mixture was stirred a room temperature overnight. m-Chloroperbenzoic acid was further added thereto, and the mixture was stirred again at room temperature overnight. The reaction mixture was washed successively with 10% aqueous sodium thiosulfate solution, a saturated aqueous sodium hydrogen carbonate solution, and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1-1:2) to give a sulfoxide compound 26 (295 mg). APCI-Mass m/Z 622/624 ($M+NH_4$).

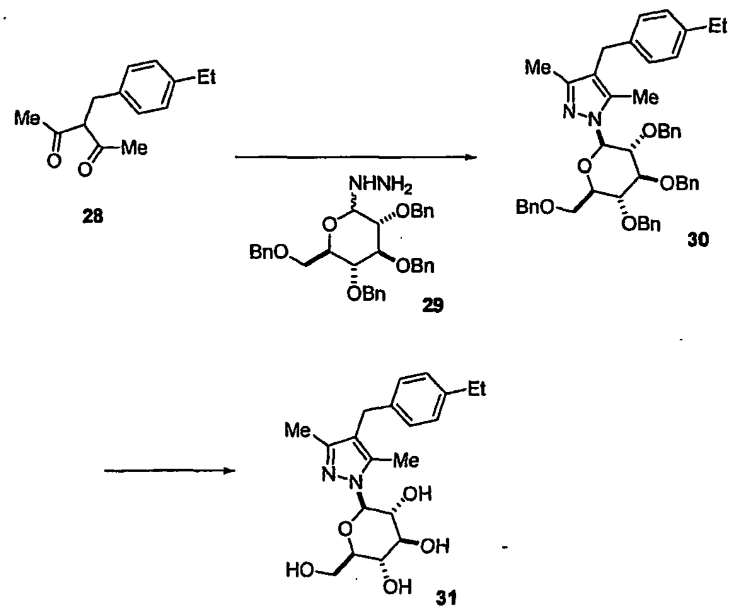
(3) The above sulfoxide compound 26 (293 mg) was dissolved in a mixture of methanol (10 ml) - tetrahydrofuran (5ml), and sodium methoxide (28% methanol solution, 2 drops) was added thereto, and the mixture was stirred at room temperature for one hour. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol = 9:1) to give 1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxybenzo[b]thiophen-2-ylmethyl)benzene as pale yellow powder. APCI-Mass m/Z 454/456 ($M+NH_4$).

Example 107 1-(β-D-glucopyranosyl)-4-chloro-3-(1,1-dioxybenzo[b]thiophen-2-ylmethyl)benzene

The target compound was prepared in a manner similar to Example 106. APCI-Mass m/Z 470/472 ($M+NH_4$).

Example 108

3,5-dimethyl-4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)pyrazole



In the above scheme, the symbols are as defined above.

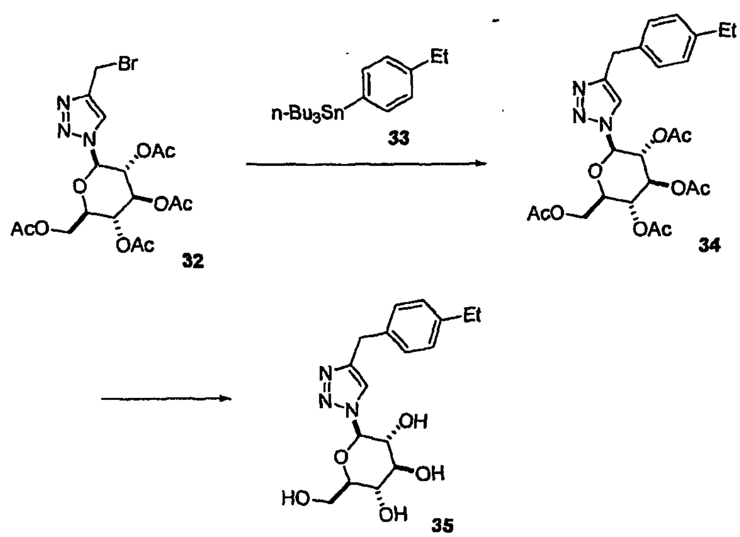
(1) 3-(4-ethylphenylmethyl)-2,4-pentanedione 28 (700 mg) and 2,3,4,6-tetra-O-benzyl-α,β-D-glucosehydrazone 29 (1.70 g)(See Schmidt, R. R. et al., *Liebigs Ann. Chem.* 1981, 2309) were dissolved in tetrahydrofuran (20 ml), and the mixture was stirred at room temperature for 18 hours under argon atmosphere. The solvent was evaporated under reduced pressure, and the residue was dissolved in toluene (20 ml), and the mixture was heated with stirring under reflux for 2 hours. The mixture was left alone until it was cooled, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 90:10 - 65:35)

to give 3,5-dimethyl-4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)pyrazole 30 (299 mg) as a pale yellow semisolid. APCI-Mass m/Z 737 (M+H).

(2) The above tetrabenzyl compound 30 (294 mg) was dissolved in a mixture of ethanol (5 ml) and tetrahydrofuran (4 ml), and added thereto was palladium hydroxide (100 mg), and the mixture was stirred at room temperature for 16 hours under hydrogen atmosphere under normal pressure. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The residue was crystallized from diethyl ether to give the desired 3,5-dimethyl-4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)pyrazole 31 (118 mg) as colorless powder. APCI-Mass m/Z 377 (M+H).

Example 109

4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-1,2,3-triazole



In the above scheme, n-Bu is n-butyl group, and other symbols are as defined above.

(1) A solution of

4-(bromomethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,3-triazole 32 (500 mg) (See Federico G. H. et al., *J. Med. Chem.* (1979) 29, 496), tri-n-butyl(4-ethylphenyl)tin 33 (604 mg) and tetrakis(triphenylphosphine)palladium (0) (59 mg) in tetrahydrofuran (10 ml) was stirred under heating at 70°C for 12 hours under argon atmosphere. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and then, an aqueous potassium fluoride solution was added thereto and the mixture was stirred at room temperature for one hour. Insoluble materials were filtered off, and the filtrate was washed with water, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 90:10 - 50:50) to give 4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,3-triazole 34 (90 mg) as a colorless solid.

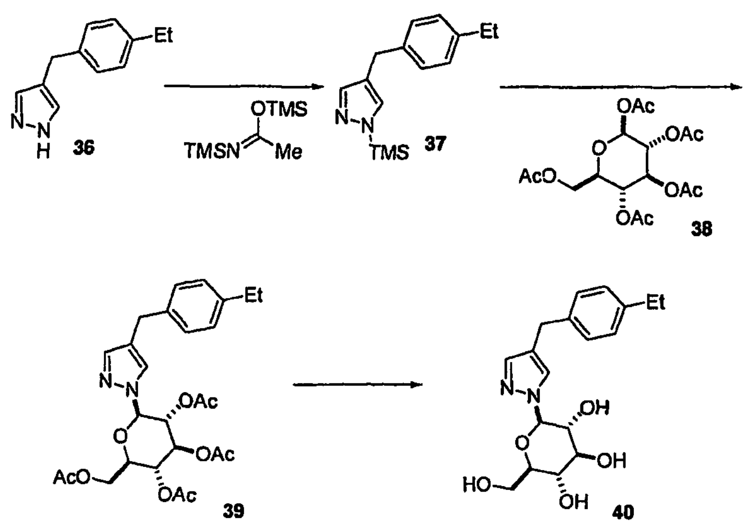
APCI-Mass m/Z 518 (M+H).

(2) From the above tetraacetate compound 34, the desired 4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-1,2,3-triazole 35 was prepared in a manner similar to Example 106-(3) as a colorless solid.

APCI-Mass m/Z 350 (M+H).

Example 110

4-(4-Ethylphenylmethyl)-1-(β-D-glucopyranosyl)pyrazole



In the above scheme, TMS is a trimethylsilyl group, and other symbols are as defined above.

(1) To a solution of 4-(4-ethylphenylmethyl)pyrazole 36 (495 mg) in acetonitrile (2.0 ml) was added N,O-bis(trimethylsilyl)acetamide (1.05 ml), and the mixture was stirred under heating at 60°C for 2.5 hours under argon atmosphere. The reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure to give crude 4-(4-ethylphenylmethyl)-1-trimethylsilylpyrazole 37, which was used in the subsequent reaction without further purification.

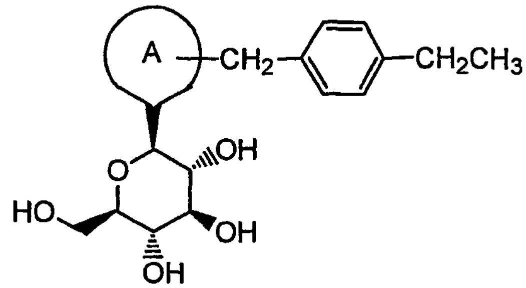
(2) The above N-silyl compound 37 was dissolved in dichloroethane (7.0 ml), and added thereto were molecular sieve 4A powder (500 mg), 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose 38 (1.04 g) and trimethylsilyl trifluoromethanesulfonate (0.51 ml). The mixture was stirred under heating at heating at 80°C for 3 hours under argon atmosphere. The reaction mixture was cooled to room temperature, and insoluble materials were filtered off. Subsequently, the filtrate was poured into a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted twice with dichloromethane, and dried over sodium sulfate. The

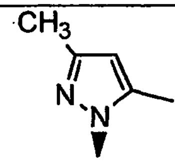
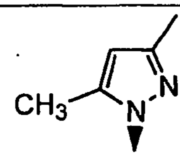
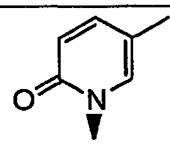
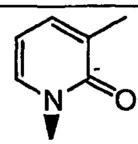
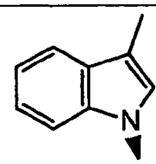
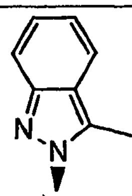
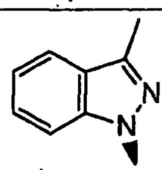
solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 80:20 - 50:50) to give 4-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)pyrazole 39 (610 mg) as a colorless semisolid. APCI-Mass m/Z 517 (M+H).

(3) From the above tetraacetate compound 39, the desired 4-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)pyrazole 40 was prepared in a manner similar to Example 106-(3) as colorless oil. APCI-Mass m/Z 349 (M+H).

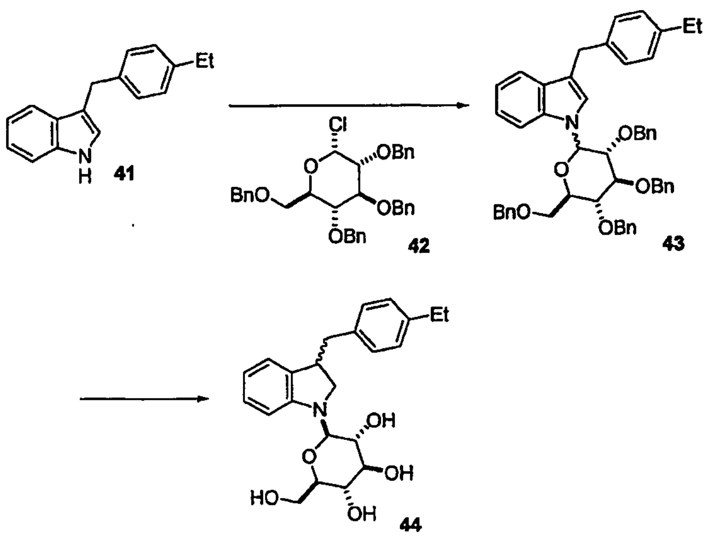
In a manner similar to Example 110, the compounds shown in Table 3 below were prepared from corresponding starting materials.

Table 3



Examples	Ring A	APCI-Mass (m/Z)
111		363(M+H)
112		363(M+H)
113		376(M+H)
114		393(M+NH4)
115		415(M+NH4)
116		399(M+H)
117		399(M+H)

Example 118 3-*RS*-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-2,3-dihydroindole



In the above scheme, the symbols are as defined above.

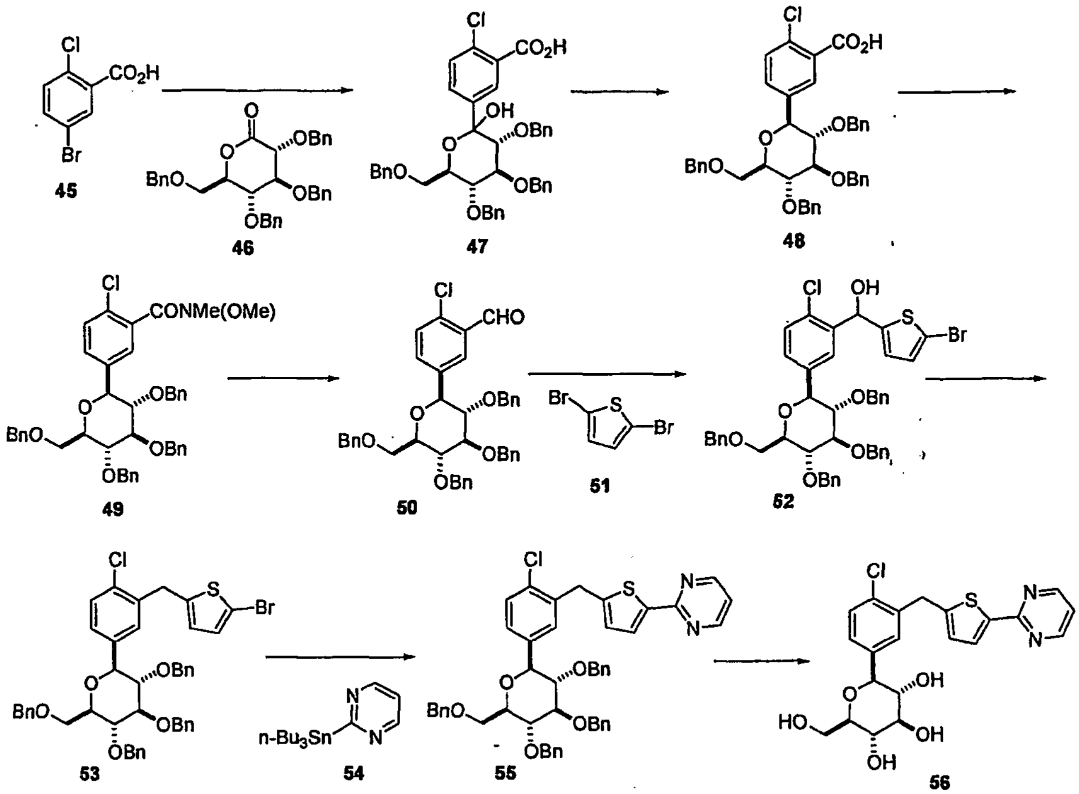
(1) To a suspension of potassium hydroxide power (953 mg) and sodium sulfate (6.0 g) in acetonitrile (50 ml) was added 3-(4-ethylphenylmethy)-1H-indole 41 (500 mg), and the mixture was stirred at room temperature for one hour under argon atmosphere. To the reaction mixture was added a solution of benzylchloro-α-D-glucose 42 (3.0 g) (see Cicchillo R. M. et al., *Carbohydrate Research* (2000) 328, 431) in acetonitrile (20 ml), and the mixture was stirred at room temperature overnight. The reaction mixture was poured into 2N aqueous hydrochloric acid solution, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 - 85:15) to give 3-(4-ethylphenylmethyl)-1-(2,3,4,6-tetra-O-benzyl-αβ-D-glucopyranosyl)-1H-indole 43 (1.04 g) as a pale yellow syrup. APCI-Mass m/Z 758 (M+H).

(3) From the above tetrabenzyl compound 43, the desired 3-*RS*-(4-ethylphenylmethyl)-1-(β-D-glucopyranosyl)-

-2,3-dihydroindole 44 was prepared in a manner similar to Example 108-(2) as pale pink powder. APCI-Mass m/Z 400 (M+H).

Example 119

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene



In the above scheme, the symbols are as defined above.

(1) To a solution of 5-boromo-2-chlorobenzoic acid 45 (1.22 g) in a mixture of tetrahydrofuran (20 ml) - toluene (20 ml) was added dropwise n-butyl lithium (2.44 M hexane solution, 4.26 ml) at -78°C under argon atmosphere. The mixture was stirred at -78°C for 30 minutes, and added dropwise thereto was a solution of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone 46 (2.16 g) in toluene (10 ml), and the mixture was further stirred at the same temperature for 2 hours. To the mixture was added a saturated aqueous ammonium chloride solution, and the mixture was warmed to room temperature. The reaction mixture was made acidic by addition of 10% aqueous hydrochloric acid solution,

and extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a crude compound 47 as oil, which was used in the subsequent step without further purification.

(2) The above crude compound 47 was dissolved in dichloromethane (30 ml), and thereto were added dropwise triisopropylsilane (2.46 ml) and boron trifluoride · diethyl ether complex (1.52 ml) at -78°C. Subsequently, the mixture was stirred at 0°C for one hour, and added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was further stirred for 20 minutes. The reaction mixture was made acidic by addition of 10% aqueous hydrochloric acid solution, and extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (chloroform:methanol = 100:1 - 50:1) to give a compound 48 (1.41 g) as oil.

(3) The compound 48 (1.41 g) was dissolved in dichloromethane (10 ml), and added thereto was oxalyl chloride (2ml). The mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride. The compound was dissolved in chloroform (10 ml), and added dropwise to a solution of N,O-dimethylhydroxyamine hydrochloride (390 mg) and triethyl amine (1.12 ml) in chloroform (10 ml) at 0°C. The mixture was stirred at room temperature overnight, and the reaction mixture was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1-2:1) to give a compound 49 (784 mg)

as pale yellow oil. APCI-Mass m/Z 739/741 ($M+NH_4$).

(4) The compound 49 (1.22 g) was dissolved in tetrahydrofuran (20 ml), and the mixture was cooled to -78°C under argon atmosphere. To the mixture was added dropwise diisobutylaluminum hydride (1.0 M toluene solution, 4.2 ml), and the mixture was stirred at the same temperature for 3 hours. Added thereto was 10% aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to give a compound 50 (771 mg) as pale yellow oil. APCI-Mass m/Z 680/682 ($M+NH_4$).

(5) 2,5-dibromothiophene 51 (1.31 g) was dissolved in tetrahydrofuran (30 ml) and the mixture was cooled to -78°C under argon atmosphere. To the mixture was added dropwise n-butyl lithium (2.59 M hexane solution, 2.01 ml), and the mixture was stirred at the same temperature for 30 minutes. Added dropwise thereto was a solution of the above compound 50 (2.40 g) in tetrahydrofuran (15 ml), and the mixture was stirred at -78°C for 2 hours. Added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate and washed with brine. The extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1 - 4:1) to give a compound 52 (2.62 mg) as pale brown oil. APCI-Mass m/Z 842/844 ($M+NH_4$).

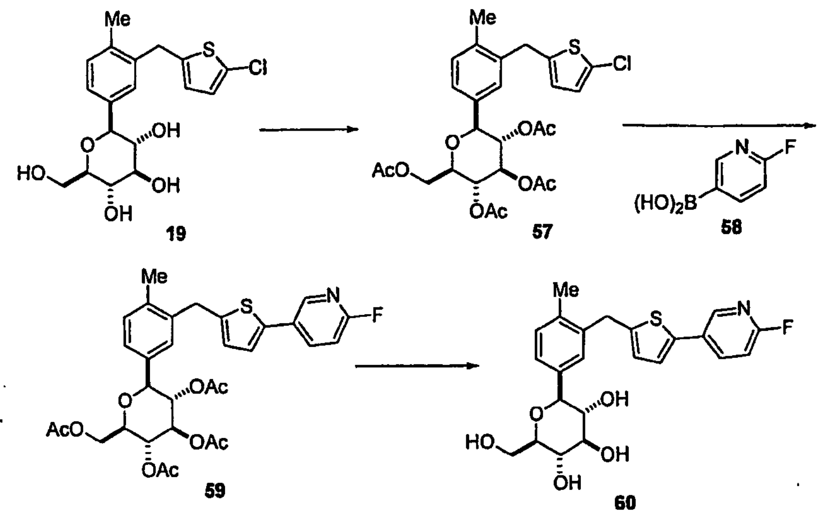
(6) The compound 52 was treated in a manner similar to Example 3- (2) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl) -3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 53 as a pale yellow solid. APCI-Mass m/Z 826/828 ($M+NH_4$).

(7) A mixed solution of the above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl) -3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 53 (200 mg), tri-n-butyl(2-pyrimidinyl)tin 54 (137 mg) and bis(triphenylphosphine)palladium (II) dichloride (9 mg) in N-methyl-2-pyrrolidinone (5 ml) was stirred at 100°C four 7 hours under argon atmosphere. The mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and subsequently with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. . The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1 - 2:1) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene 55 (93 mg) as pale brown oil. APCI-Mass m/Z 826/828 ($M+NH_4$).

(8) To a solution of the above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene 55 (90 mg) in ethanethiol (1.5 ml) was added boron trifluoride · ether complex (0.42 ml) at 0°C, and the mixture was stirred at room temperature overnight. The mixture was cooled again to 0°C, and added thereto were a saturated aqueous sodium hydrogen carbonate solution and an aqueous sodium thiosulfate solution. The mixture was extracted with ethyl acetate and tetrahydrofuran, and the extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol = 19:1 - 9:1) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene 56 (27 mg) as pale yellow powder. APCI-Mass m/Z 449/451 (M+H).

Example 120

1-(β-D-glucopyranosyl)-3-(6-(2-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene



In the above scheme, the symbols are as defined as above.

(1) The compound 19 obtained in Example 4 was treated in a manner similar to Example 106- (1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 as colorless crystals. APCI-Mass m/Z 570/572 ($M+NH_4$).

(2) A solution of the above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (200 mg), 6-fluoropyridine-3-boronic acid 58 (117 mg), tri-tert-butylphosphine·tetrafluoroboric acid adduct (24 mg), potassium fluoride (80 mg) and tris(dibenzylideneacetone) dipalladium (0) (27 mg) in tetrahydrofuran (8 ml) was stirred at room temperature for 2 days under argon atmosphere. Added thereto was a saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 90:10 - 70:30) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene 59

(44 mg) as colorless crystals. APCI-Mass m/Z 631 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5--(6-fluoro-3-pyridyl)-2-thienylmethyl)-4-methylbenzene 59 (39 mg) was dissolved in 1,4-dioxane (4 ml)-tetrahydrofuran (4 ml), and added thereto was 2N sodium hydroxide (2 ml). The mixture was stirred at room temperature for one hour. The mixture was made acidic by addition of an aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and then dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the desired 1-(β-D-glucopyranosyl)-3-(5-(6-fluoro-3-pyridyl)-2-thienyl-methyl)-4-methylbenzene 60 (34 mg) as colorless powder. APCI-Mass m/Z 463 ($M+NH_4$).

Example 121

1-(β-D-glucopyranosyl)-4-chloro-3-(2-(5-phenyl-2-thienyl)ethyl)benzene

The target compound was obtained in a manner similar to Example 1, from 5-bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl)-benzene. APCI-Mass m/Z 478/480 ($M+NH_4$).

Example 122

1-(β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120 (1) and 3-dimethylaminophenylboronic acid were used and treated in a manner similar to Example 120- (2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methylbenz

ene. APCI-Mass m/Z 638 (M+H).

(2) the above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-dimethylaminophenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the target compound. APCI-Mass m/Z 470 (M+H).

Example 123

1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene

(1) A mixed solution of 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 53 (1.24 g) obtained in Example 119 -(6), 3-cyanophenylboronic acid (270 ml), bis(triphenylphosphine)palladium (II) dichloride (54 mg) and 2M aqueous sodium carbonate solution (2.3 ml) in 1,2-dimethoxyethane (12 ml) was heated under reflux for 4 hours. The mixture was diluted with ethyl acetate and washed successively with a saturate aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 7:1 - 5:1) to give 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene (1.12 g) as colorless oil. APCI-Mass m/Z 849/851 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-cyanophenyl)-2-thienylmethyl)benzene was used and treated in a manner similar to Example 3-(3) to give the target compound as colorless powder. APCI-Mass m/Z 489/491 ($M+NH_4$).

Example 124

1-(β-D-glucopyranosyl)-4-methyl-3-(5-(5-pyrimidinyl)-2-thienylmethyl)benzene

(1) A mixed solution of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (600 mg) obtained in Example 120-(1), tri-n-butyl(5-pyrimidinyl)tin (600 mg), tri-tert-butylphosphine·tetrafluoroboric acid adduct (116 mg), cesium fluoride (414 mg), and tris(dibenzylideneacetone) dipalladium (0) (91 mg) in 1,4-dioxane (18 ml) was heated under reflux at 100°C for 3 hours under argon atmosphere. Insoluble materials were filtered off, and the filtrate was diluted with ethyl acetate and washed with brine. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 75:25 - 40:60) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(5-(5-pyrimidinyl)-2-thienylmethyl)benzene (266 mg) as colorless crystals. APCI-Mass m/Z 597 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(5-(5-pyrimidinyl)-2-thienylmethyl)benzene was used and treated in a manner similar to Example 106-(3) to give the target compound as colorless powder. APCI-Mass m/Z 429 (M+H).

<u>Example 125</u>

<u>1-(β-D-glucopyranosyl)-4-chloro-3-(2-phenyl-5-thiazolylmethylbenzene</u>

The target compound was prepared in a manner similar to Example 1, starting from 5-bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl)benzene. APCI-Mass m/Z 448/450 (M+H).

<u>Example 126</u>

<u>1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-pyridyl)-2-thienyl-methyl)benzene</u>

(1) 1-(β-D-glucopyranosyl) -4-chloro-3-(5-chloro-2-thienylmethyl)benzene obtained in Example 19 was used and treated in a manner similar to Example 106-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)4-chloro-3-(5-chloro-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 590/592 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-chloro-2-thienylmethyl)benzene and tri-n-butyl(3-pyridyl)tin were used and treated in a manner similar to Example 124 to give the target compound as colorless powder. APCI-Mass m/Z 448/450 (M+H).

Example 127

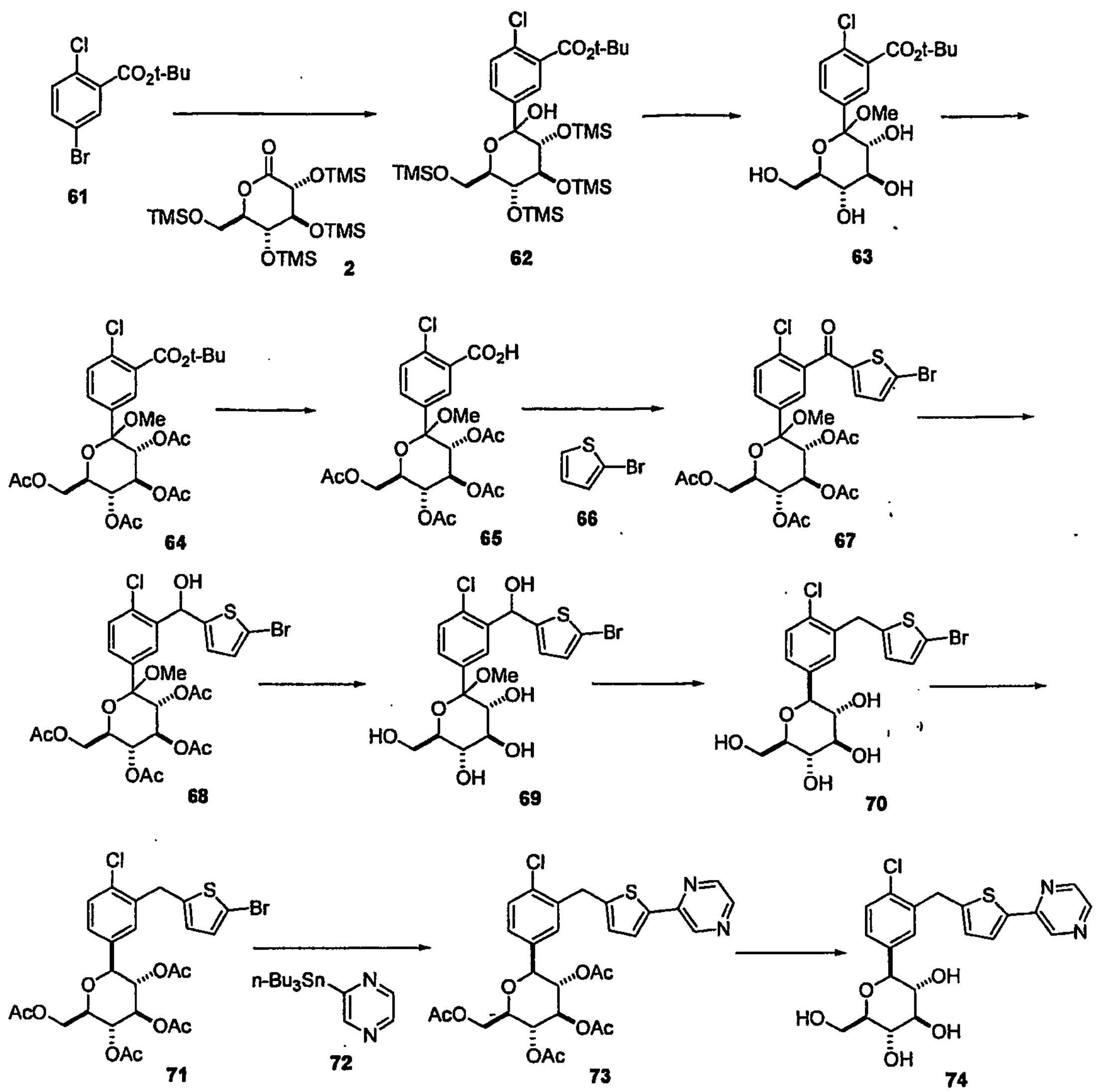
1-(β-D-glucopyranosyl)-3-(5-(3-cyanophenyl)-2-thienyl-methyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) -3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120-(1) and 3-cyanophenylboronic acid were used and treated in a manner similar to Example 120-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5—(3-cyano phenyl)-2-thienylmethyl)-4-methylbenzene. APCI-Mass m/Z 637 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5—(3-cyano phenyl)-2-thienylmethyl)-4-methylbenzene was used and treated in a manner similar to Example 106-(3) to give the target compound as colorless powder. APCI-Mass m/Z 469 ($M+NH_4$).

Example 128

1-(β-D-glucopyranosyl)—4-chloro-3-(5-pyrazinyl-2-thienyl-methyl)benzene



In the above scheme, the symbols are as defined above.

(1) A solution of mesityl bromide (4.74 g) in tetrahydrofuran (100 ml) was cooled to -78°C under argon atmosphere, and thereto was added dropwise t-butyl lithium (1.43 M pentane solution, 33 ml). The mixture was stirred at -30 to -20°C for one hour, and then, a mixed solution of t-butyl 5-bromo-2-chlorobenzoate 61 (4.94 g) and 2,3,4,6-tetrakis-O-trimethylsilyl-D-glucono-1,5-lactone 2 (see USP 6,515,117) (11.10 g) in tetrahydrofuran (70 ml) was added dropwise thereto at -78°C. The mixture was stirred at the same temperature for one hour to give a compound 62. Without isolating this compound, a solution of methanesulfonic acid

(3.75 ml) in methanol (50 ml) was added to the reaction solution, and the mixture was stirred at room temperature for 18 hours. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution at 0°C, and the mixture was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol = 19:1) to give a methyl ether compound 63 (4.55 g) of the lactol as pale yellow powder. APCI-Mass m/Z 422/424 ($M+NH_4$).

(2) The compound 63 was treated in a manner similar to Example 106-(1) to give the compound 64. APCI-Mass m/Z 590/592 ($M+NH_4$).

(3) A solution of the above compound 64 (7.10 g) in formic acid (50 ml) was stirred at 50°C for 30 minutes. The solvent was evaporated under reduced pressure, and the residue was subjected to azeotropic distillation with toluene, twice, to give a compound 65 as colorless powder. Without further purification, this compound was dissolved in dichloromethane (50 ml). Added thereto were oxalyl chloride (1.3 ml) and N,N-dimethylformamide (one drop), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give a corresponding acid chloride, which was dissolved in dichloroethane (50 ml), without further purification. To the solution was added 2-bromothiophene 66 (2.63 g) and the mixture was cooled to 0°C. Added gradually thereto was aluminum chloride (8.26 g), and subsequently, the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was poured into ice-cold water, and the mixture was extracted with ethyl acetate. The extract was washed successively with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl

acetate =10:1-5:1) to give a compound 67 (7.01 g) as pale yellowish powder. APCI-Mass m/Z 678/680 ($M+NH_4$).

(4) The above ketone compound 67 (7.01 g) was dissolved in ethanol (50 ml), and thereto was added sodium borohydride (401mg), and the mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed with successively with water, 2N aqueous hydrochloride acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a compound 68 as pale yellow powder, which was dissolved in methanol (50 ml) without further purification. To the solution, sodium methoxide (28% methanol solution, 5 drops) was added, and then the mixture was stirred at room temperature for 2.5 hours. The solvent was evaporated under reduced pressure to give a deacetylated compound 69 as pale yellow powder. Without further purification, it was dissolved in dichloromethane (170 ml) - acetonitrile (70 ml), and added thereto was triethylsilane (10.2 ml), and the mixture was cooled to 0°C. Added dropwise thereto was boron trifluoride · diethyl ether complex (8.1 ml), and the mixture was stirred at room temperature for 5 hours. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a crude 1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)4-chlorobenzene 70 as pale brown powder. Without further purification, this was dissolved in dichloromethane (30 ml), and added thereto were acetic anhydride (10.0 ml), pyridine (8.57 ml) and 4-dimethylaminopyridine (258 mg), and the mixture was stirred at room temperature for one hour. The solvent was evaporated

under reduced pressure, and the residue was dissolved in ethyl acetate, and the solution was washed successively with water, 1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The solution was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)4-chlorobenzene 71 (3.17 g) as colorless crystals. APCI-Mass m/Z 634/636 ($M+NH_4$).

(5) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)4-chlorobenzene 71 (600 mg) was dissolved in 1,4-dioxane (11 ml). Added thereto were tri-n-butyl(pyrazinyl)tin 72 (720 mg), tetrakis(triphenylphosphine)palladium (0) (206 mg) and copper (I) iodide (51 mg), and the mixture was stirred under heating at 100°C for 1.5 hours, under irradiation by a microwave (500 W). The mixture was diluted with ethyl acetate, the insoluble materials were filtered off, and the filtrate was washed with water. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate =75:25-30:70), and crystallized from hexane-diethyl ether to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene 73 (263 mg) as pale yellow crystals. APCI-Mass m/Z 617/619 (M+H).

(6) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene 73 was used and treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-pyrazinyl-2-thienylmethyl)benzene 74 as colorless powder. APCI-Mass m/Z 449/451

(M+H).

Example 129

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene was used and treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 482/484 $(M+NH_4)$.

Example 130

1-(β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 obtained in Example 120-(1) and 3-formylphenylboronic acid were used and treated in a manner similar to Example 120- (2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-formylphenyl)-2-thienylmethyl)-4-methylbenzene. APCI-Mass m/Z 640 $(M+NH_4)$.

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-formylphenyl)-2-thienylmethyl)-4-methylbenzene (100 mg) was dissolved in dichloromethane (2 ml), and added thereto was (diethylamino)sulfur trifluoride (0.30 ml). The mixture was stirred at room temperature overnight. Water was added to the mixture and the mixture was extracted with chloroform. The extract was washed with brine and dried over magnesium sulfate, and then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate =9:1-1:1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene (82 mg). APCI-Mass m/Z 662 $(M+NH_4)$.

(3) The above obtained

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene was used and treated in a manner similar to Example 120-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 494 ($M+NH_4$).

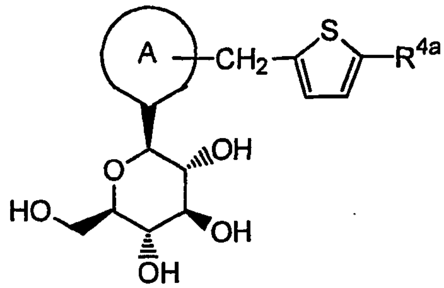
Example 131

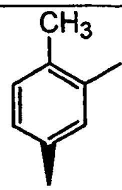
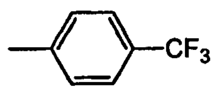
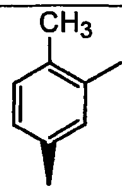
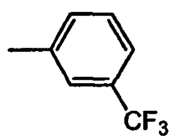
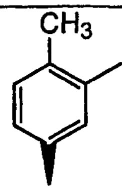
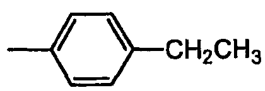
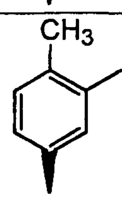
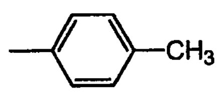
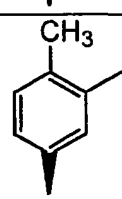
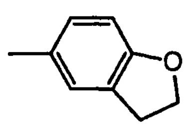
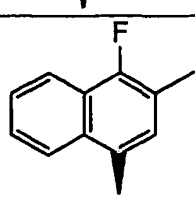
1-(β-D-glucopyranosyl)-4-chloro-3-(6-phenyl-3-pyridylmethyl)benzene

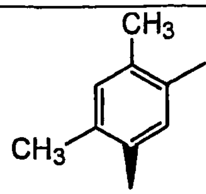
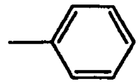
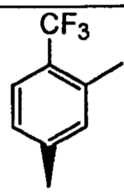
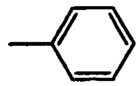
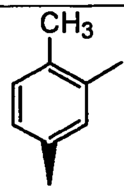
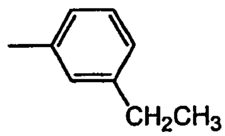
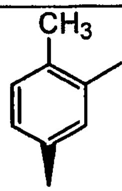
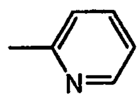
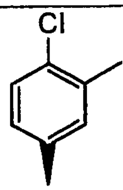
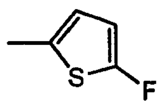
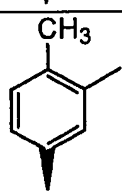
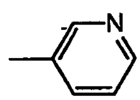
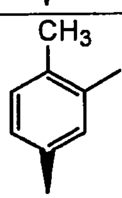
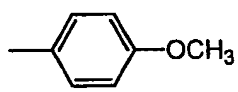
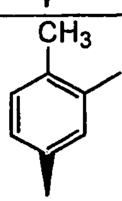
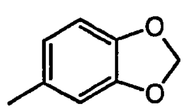
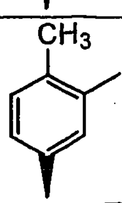
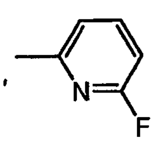
5-Bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl)benzene was used and treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 442/444 (M+H).

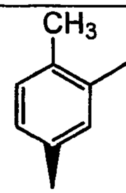
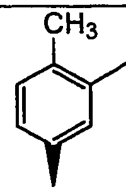
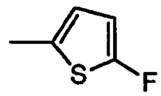
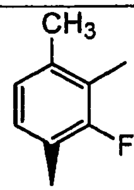
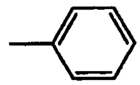
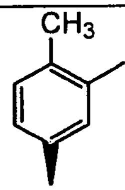
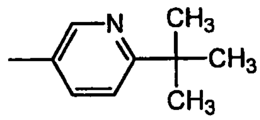
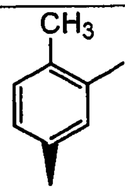
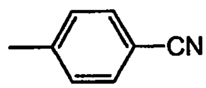
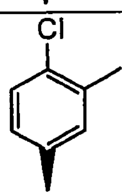
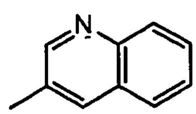
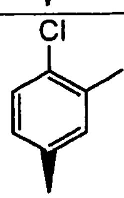
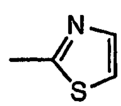
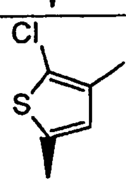
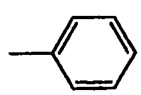
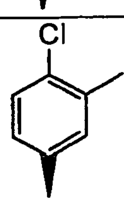
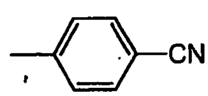
In a manner similar to the method disclosed in any of the above Examples, the compounds shown in Table 4 below were prepared from corresponding starting materials. The numbers shown in a column of "preparation method" in the Table indicates the Example number, according to which the preparation was carried out in the similar manner.

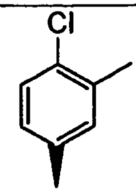
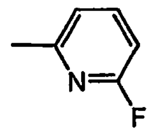
Table 4



Examples	Ring A	R^{4a}	Preparation Method	APCI-Mass (m/Z)
1 3 2			1	512 (M+NH_4)
1 3 3			1	512 (M+NH_4)
1 3 4			4	472 (M+NH_4)
1 3 5			4	458(M+NH_4)
1 3 6			4	486(M+NH_4)
1 3 7		Cl	1	456/458(M+NH_4)

1 3 8			2	458(M+NH4)
1 3 9			2	498(M+NH4)
1 4 0			1	472(M+NH4)
1 4 1			1	428(M+H)
1 4 2			4	488/490(M+NH4)
1 4 3			1	428(M+H)
1 4 4			1	474(M+NH4)
1 4 5			1	488(M+NH4)
1 4 6			1	463(M+NH4)

147		CF_3	1	436(M+NH4)
148			1	468(M+NH4)
149			1	462(M+NH4)
150			103	484(M+H)
151			124	469(M+NH4)
152			122	498/500(M+H)
153			128	454/456(M+H)
154			2	470/472(M+NH4)
155			122	489/491(M+NH4)

156			122	466/468(M+H)

Example 157 1-(β-D-glucopyranosyl)-4-chloro-3-(6-isopropyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-isopropyloxybenzo[b]thiophen-2-ylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 496/498 ($M+NH_4$).

Example 158 1-(β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-chloro-2-thienylmethyl)-4-methylbenzene 57 (12.0 g) obtained in Example 120-(1) was dissolved in tetrahydrofuran (120 ml) and methanol (360 ml), and added thereto were triethylamine (24.2 ml) and 10% palladium carbon catalyst (wet, 3.6 g), and the mixture was stirred at room temperature for 18 hours under hydrogen atmosphere under normal pressure. The insoluble materials were filtered off, washed with tetrahydrofuran, and the filtrate was evaporated under reduced pressure. The residue was dissolved in chloroform, washed successively with a 5% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution and water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was recrystallized from ethanol to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene (7.79 g) as colorless crystals. APCI-Mass m/Z 536 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl3-(2-thienylmethyl)benzene was treated in a manner similar to Example 106-(3) to give the

desired 1-(β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 368 ($M+NH_4$).

Example 159 1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-methyl-3-(2-thienylmethyl)benzene (11.08 g) obtained in Example 158-(1) was dissolved in chloroform (100 ml), and added dropwise thereto at 0°C was a solution of bromine (3.71 g) in chloroform (13 ml). The mixture was stirred at 0°C for 1.5 hours, and then, at room temperature for 1 hour, and the mixture was poured into a 10% aqueous sodium thiosulfate solution and a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted twice with chloroform, washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 80:20 - 67:33) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene (7.13 g) as a colorless solid. APCI-Mass m/Z 614/616 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 446/448 ($M+NH_4$).

Example 160 1-(β-D-glucopyranosyl)-3-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 3-bromobenzadlehyde was treated in a manner similar to Example 4 to give the target compound. APCI-Mass m/Z 430 ($M+NH_4$).

Example 161 1-(β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene (500 mg) obtained in Example 159-(1) was dissolved in N,N-dimethylacetamide (10 ml), and added thereto were zinc cyanide (98 mg), tris(dibenzylideneacetone)dipalladium(0) (77 mg), 1,1'-bis(diphenylphosphino)ferrocene (47 mg) and zinc power (14 mg). The mixture was heated under stirring at 120°C overnight. The reaction solution was cooled, diluted with ethyl acetate and water, and the insoluble materials were filtered off. The organic layer of the filtrate was washed twice with water and successively washed with brine. After drying the same over sodium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 - 50:50) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene (207 mg) as colorless crystals. APCI-Mass m/Z 561 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-cyano-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 393 ($M+NH_4$).

Example 162 1-(β-D-glucopyranosyl)-4-fluoro-3-(5-(2-pyridyl)-2-thienylmethyl)naphthalene

4-Bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl)naphthalene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 482 (M+H).

Example 163 1-(β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) was treated in a manner similar to Example 106-(3) to give the target compound. APCI-Mass m/Z 466/468 ($M+NH_4$).

Example 164 1-(β-D-glucopyranosyl)-4-methyl-3-(5-(2-pyrimidinyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and tri-n-butyl(2-pyrimidinyl)tin 54 were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 429 (M+H).

Example 165 1-(β-D-glucopyranosyl)-4-methyl-3-(5-(2-thiazolyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and tri-n-butyl(2-thiazolyl)tin were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 434 (M+H).

Example 166 1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethyl-3-pyridylmethyl)benzene

5-Bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 394/396 (M+H).

Example 167 1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethylbenzo[b]thiophen-2-ylmethyl)benzene

6-Ethylbenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde

obtained in Reference Example 16-(1) were treated in a manner similar to Example 4 to give the target compound. APCI-Mass m/Z 466/468 (M+H).

Example 168 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 (500 mg) obtained in Example 128-(4) was dissolved in 1,2-dimethoxyethane (15 ml), and added thereto were 6-fluoropyridine-3-boronic acid 58 (228 mg), tetrakis(triphenylphosphine)palladium(0) (94 mg) and cesium fluoride (738 mg). The mixture was heated under reflux for 30 minutes. The reaction solution was poured into a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 75:25 - 60:40) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene (454 mg) as a colorless solid. APCI-Mass m/Z 634/636 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-fluoro-3-pyridyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 483 ($M+NH_4$), 466 (M+H).

Example 169 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-methoxy-3-pyridyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4)

and 6-methoxypyridine-3-boronic acid were treated in a manner similar to Example 168 to give the target compound. APCI-Mass m/Z 478/480 (M+H).

Example 170 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-methoxy-2-pyridyl)-2-thienylmethyl)benzene

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and tri-n-butyl(6-methoxy-2-pyridyl)tin (see Gros, Philippe; Fort, Yves. Synthesis (1999), 754-756) were treated in a manner similar to Example 128-(5) and (6) to give the target compound. APCI-Mass m/Z 478/480 (M+H).

Example 171 1-(β-D-glucopyranosyl)-4-chloro-3-(1-oxo-2-isoindolinylmethyl)benzene

5-Bromo-2-chloro-1-(1-oxo-2-isoindolynilmethyl)benzene was treated in a manner similar to Example 2 to give the target compound. APCI-Mass m/Z 437/439 ($M+NH_4$).

Example 172 1-(β-D-glucopyranosyl)-4-chloro-3-(1-phenyl-4-pyrazolylmethyl)benzene

5-Bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 431/433 (M+H).

Example 173 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and tri-n-butyl(6-ethoxy-2-pyridyl)tin (see WO 00/74681) were treated in a manner similar to Example 128-(5) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thieny

lmethyl)benzene as colorless crystals. APCI-Mass m/Z 660/662 (M+H).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene (245 mg) was dissolved in tetrahydrofuran (5 ml), added thereto was a solution of sodium hydride (oil, 9 mg) in ethanol (5 ml), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 - 90:10) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(6-ethoxy-2-pyridyl)-2-thienylmethyl)benzene (145 mg) as colorless powder. APCI-Mass m/Z 429/494 (M+H).

Example 174 1-(β-D-glucopyranosyl)-4-chloro-3-(6-n-propyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-n-propyloxybenzo[b]thiophen-2-ylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 496/498 ($M+NH_4$).

Example 175 1-(β-D-glucopyranosyl)-4-chloro-3-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)benzene was treated in a manner similar to Example 1 to give the target compound. APCI-Mass m/Z 500/502 ($M+NH_4$).

Example 176 1-(β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene from Example 159-(1) and 4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-formy

lphenyl)-2-thienylmethyl)-4-methylbenzene as a colorless solid. APCI-Mass m/Z 640 ($M+NH_4$). .

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-formylphenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 130-(2) to give the desired 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-mehylbenzene as colorless crystals. APCI-Mass m/Z 662 ($M+NH_4$).

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 494 ($M+NH_4$).

Example 177 1-(β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-methylbenzene obtained in Example 159-(1) and 3,4-difluorophenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene as colorless crystals. APCI-Mass m/Z 648 ($M+NH_4$).

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene was treated in a manner similar to Example 106-(3) to give the desired 1-(β-D-glucopyranosyl)-3-(5-(3,4-difluorophenyl)-2-thienylmethyl)-4-methylbenzene as colorless powder. APCI-Mass m/Z 480 ($M+NH_4$).

Example 178 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-

difluoromethylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and 3-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-formylphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 660/662 $(M+NH_4)$.

(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-formylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 130-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 682/684 $(M+NH_4)$.

(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 120-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(3-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless powder. APCI-Mass m/Z 514/516 $(M+NH_4)$.

Example 179 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene

(1) 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-(5-bromo-2-thienylmethyl)-4-chlorobenzene 71 obtained in Example 128-(4) and 4-formylphenylboronic acid were treated in a manner similar to Example 168-(1) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 660/662 $(M+NH_4)$.

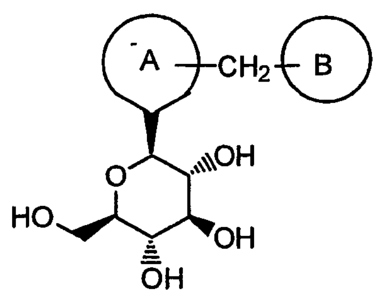
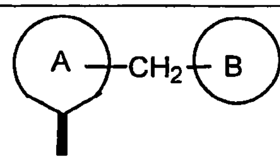
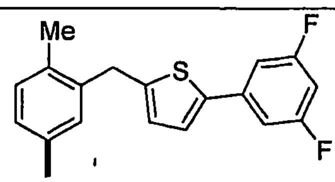
(2) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-formylphenyl)-2-

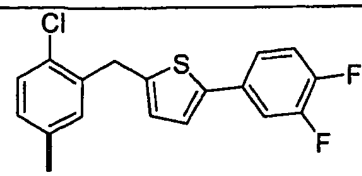
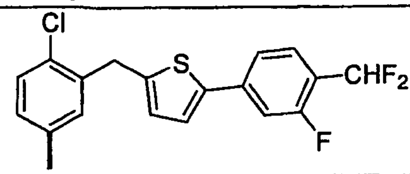
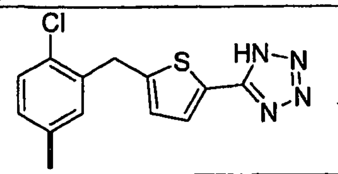
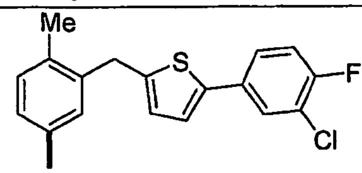
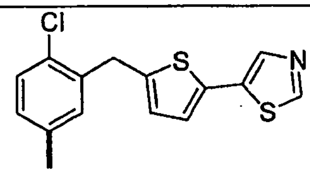
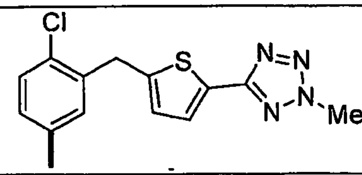
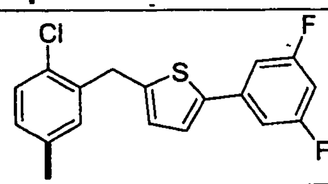
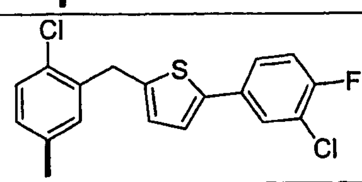
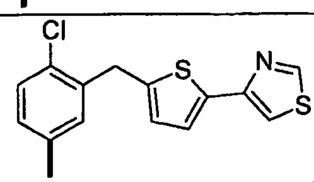
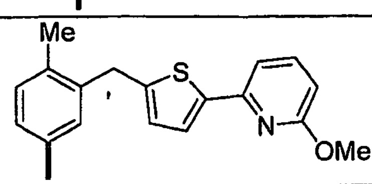
thienylmethyl)benzene was treated in a manner similar to Example 130-(2) to give 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 682/684 ($M+NH_4$).

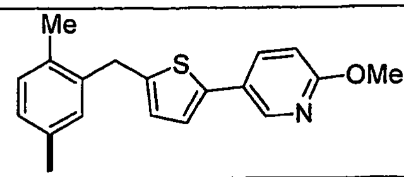
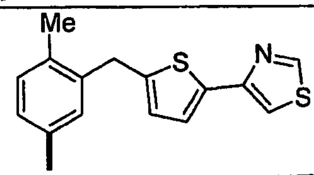
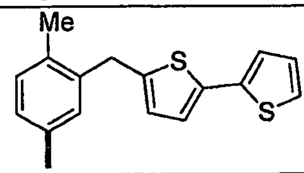
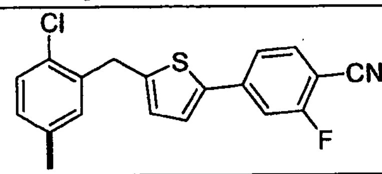
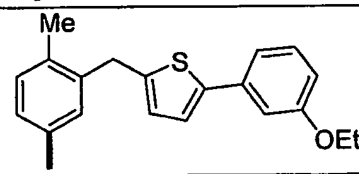
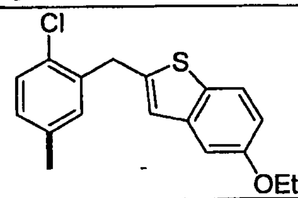
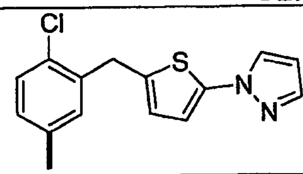
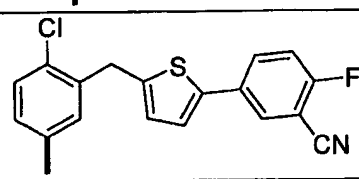
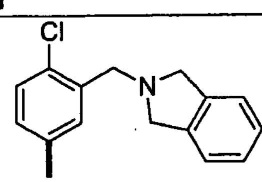
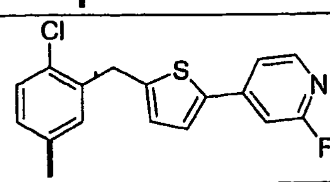
(3) The above 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)benzene was treated in a manner similar to Example 120-(3) to give the desired 1-(β-D-glucopyranosyl)-4-chloro-3-(5-(4-difluoromethylphenyl)-2-thienylmethyl)-benzene as colorless powder. APCI-Mass m/Z 514/516 ($M+NH_4$).

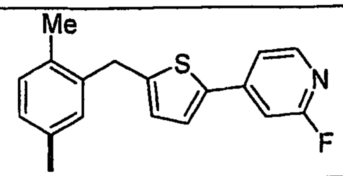
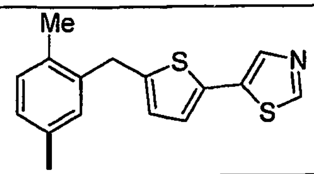
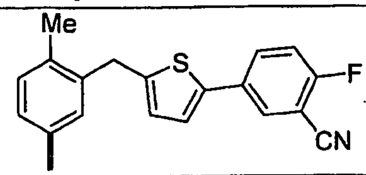
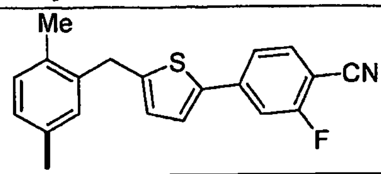
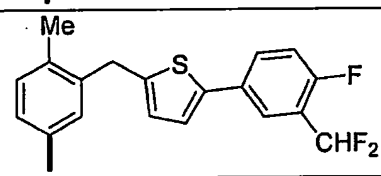
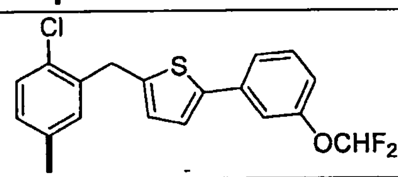
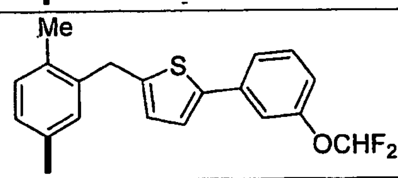
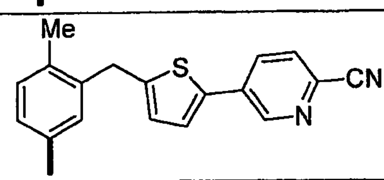
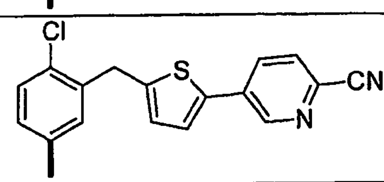
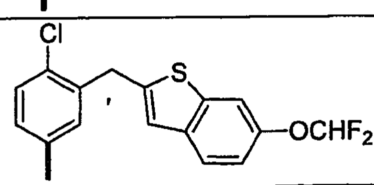
The compounds shown in Table 5 below were prepared in a manner similar to one of the above Examples from the corresponding starting materials.

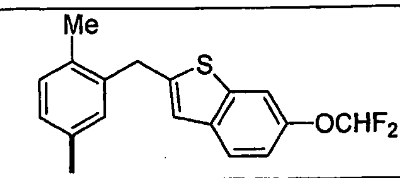
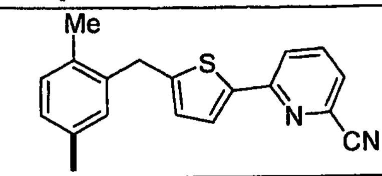
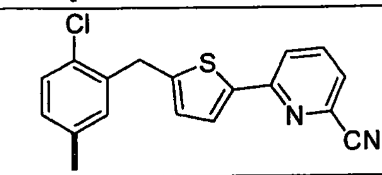
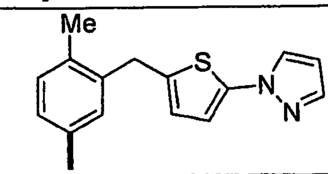
Table 5

		
Examples		APCI-Mass (m/Z)
180		480 ($M+NH_4$)

181		500/502 (M+NH4)
182		532/534 (M+NH4)
183		437/439* (M-H) (*ESI-Mass)
184		496/498 (M+NH4)
185		454/456 (M+H)
186		470/472 (M+NH4)
187		500/502 (M+NH4)
188		516/518 (M+NH4)
189		454/456 (M+H)
190		458 (M+H)

191		458 (M+H)
192		434 (M+H)
193		450 (M+NH_4)
194		507/509 (M+NH_4)
195		488 (M+NH_4)
196		482/484 (M+NH_4)
197		437/439 (M+H)
198		507/509 (M+NH_4)
199		406/408 (M+H)
200		466/468 (M+H)

201		446 (M+H)
202		434 (M+H)
203		487 (M+NH$_4$)
204		487 (M+NH$_4$)
205		512 (M+NH$_4$)
206		530/532 (M+NH$_4$)
207		510 (M+NH$_4$)
208		470 (M+NH$_4$)
209		490/492 (M+NH$_4$)
210		504/506 (M+NH$_4$)

211		484 (M+NH$_4$)
212		470 (M+NH$_4$)
213		490/492 (M+NH$_4$)
214		417 (M+H)

Reference Example 1

3-Bromo-1-(5-ethyl-2-thienylmethyl)benzene

(1) A solution of 1,3-dibromobenzene (3.7 g) in tetrahydrofuran (25 ml) was cooled to -78°C under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 5.55 ml). The reaction mixture was stirred at the same temperature for 10 minutes, and thereto was added dropwise a solution of 5-ethyl-2-thiophenecarboxaldehyde (2.0 g) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated ammonium chloride solution, and the reaction mixture was warmed to room temperature. The mixture was extracted with ethyl acetate, and the extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 97:3 - 85:15) to give 3-bromophenyl-5-ethyl-2-thienylmethanol (2.97 g) as a pale yellow syrup. APCI-Mass m/Z 279/281 (M+H-H_2O).

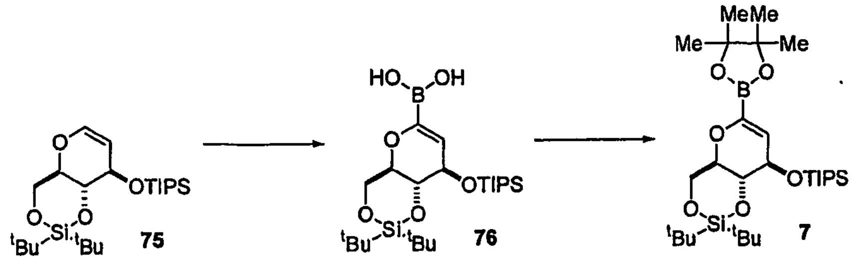
(2) The above 3-bromophenyl-5-ethyl-2-thienylmethanol (2.90 g) was dissolved in dichloromethane (38 ml), and the mixture was cooled to -78°C under argon atmosphere. To the mixture were added triethylsilane (6.18 ml) and boron trifluoride · diethyl ether complex (2.45 ml), and the mixture was gradually warmed to room temperature over a period of one hour. The mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and the dichloromethane layer was collected, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give the desired 3-bromo-(5-ethyl-2-thienylmethyl)benzene (2.57 g) as a colorless syrup. APCI-Mass m/Z 281/283 (M+H).

Reference Example 2

5-Bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one

5-Bromo-1H-pyridin-2-one (1.04 g) and 4-ethylbenzyl bromide (1.43 g) were dissolved in N,N-dimethylformamide (15 ml), and thereto was added potassium carbonate (1.66 g). The mixture was stirred at room temperature overnight, diluted with ethyl acetate, and washed successively with water and brine. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:1 - 3:1) to give 5-bromo-1-(4-ethylphenylmethyl)-1H-pyridin-2-one (1.58 g) as colorless crystals. APCI-Mass m/Z 292/294 (M+H).

Reference Example 3



In the above scheme, the symbols are as defined above.

(1) A solution of silylated glucal 75 (see Parker et al., Org. Lett. 2000, 2, 497-499) (7.00 g) in tetrahydrofuran (70 ml) was cooled to -78°C under argon atmosphere. Thereto was added dropwise t-butyl lithium (1.45 M pentane solution, 49.0 ml) over a period of 10 minutes. The mixture was stirred at the same temperature for 15 minutes, and then warmed to room temperature, and further stirred for 30 minutes. The mixture was cooled again to -78°C, and thereto was added trimethyl borate (8.90 ml) in one portion. After 15 minutes, the reaction solution was warmed to room temperature over a period of one hour, and thereto was added water (100 ml) at 0°C. The mixture was stirred for 30 minutes, and extracted twice with diethyl ether. The extract was washed with water, and then washed with brine. The resultant was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give the compound 76, which was used in the subsequent reaction without further purification.

(2) The whole amount of the above compound 76 was dissolved in toluene (65 ml), and thereto was added pinacol (2.24 g). The mixture was stirred at room temperature under argon atmosphere for 17 hours. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate, and the extract was washed with brine, dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give the compound 7 (10.4 g) as a yellow semisolid, which was used in the subsequent reaction without further purification.

APCI-Mass m/Z 569 (M+H).

Reference Example 4 5-Bromo-2-methylbenzaldehyde

(1) Methyl 5-bromo-2-methylbenzoate (see Japanese Unexamined Patent Publication No. 9-263549) (16.12 g) was dissolved in methanol (100 ml), and thereto was added 10% aqueous sodium hydroxide solution (50 ml). The mixture was stirred at 50°C for 40 minutes. Under ice-cooling, the mixture was adjusted to pH 1 by addition of 10% aqueous hydrochloric acid solution, and diluted with water. Precipitated powder was collected by filtration, and dried to give 5-bromo-2-methylbenzoic acid (14.1 g). ESI-Mass m/Z 213/215 (M-H).

(2) The above 5-bromo-2-methylbenzoic acid (10.0 g) was suspended in dichloromethane (100 ml), and thereto were added oxalyl chloride (8.1 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature for 4 hours. The solvent was evaporated under reduced pressure to give 5-bromo-2-methylbenzoyl chloride. This benzoyl chloride was dissolved in dichloromethane (200 ml), and thereto was added N,O-dimethylhydroxylamine hydrochloride (12.3 g). To the mixture was added dropwise triethylamine (20 ml) at 0°C, and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate, and washed successively with water, 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give N-methoxy-N-methyl-5-bromo-2-methylbenzamide (12.25 g) as oil. APCI-Mass m/Z 258/260 (M+H).

(3) A solution of the above N-methoxy-N-methyl-5-bromo-2-methylbenzamide (12.2 g) in tetrahydrofuran (100 ml) was cooled to -78°C under argon

atmosphere. To the mixture was added dropwise diisobutyl aluminum hydride (1.0 M toluene solution, 75 ml), and the mixture was stirred at the same temperature for one hour. 10% aqueous hydrochloric acid solution (50 ml) was added thereto, and the mixture was warmed to room temperature. The mixture was extracted with ethyl acetate twice, and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was solidified to give 5-bromo-2-methylbenzaldehyde (8.73 g). APCI-Mass m/Z 213/215 ($M+H+MeOH-H_2O$).

Reference Example 5

5-Bromo-2-chloro-1-(5-ethyl-2-thienylmethyl)benzene

(1) 5-Bromo-2-chlorobenzoic acid (5.00 g) was suspended in dichloromethane (10 ml), and thereto were added oxalyl chloride (2.2 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature for 6 hours. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzoyl chloride. This compound and 2-ethylthiophene (2.38 g) were dissolved in dichloromethane (20 ml), and thereto was added aluminum chloride (3.11 g) at 0°C. The mixture was stirred at the same temperature for one hour. The reaction mixture was poured into a cold 10% aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with 10% aqueous hydrochloric acid solution, water, a saturated aqueous sodium hydrogen carbonate solution, and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:1) to give 5-bromo-2-chlorophenyl 5-ethyl-2-thienyl ketone (5.29 g) as an oil. APCI-Mass m/Z 329/331 (M+H).

(2) A solution of the above 5-bromo-2-chlorophenyl 5-ethyl-2-thienyl ketone (5.29 g) in dichloromethane (50 ml) - acetonitrile (50 ml) was cooled under ice-cooling, and thereto were added dropwise triethylsilane (7.69 ml) and boron trifluoride · diethyl ether complex (6.1 ml). Subsequently, the mixture was stirred at room temperature for 3.5 hours, and was cooled again under ice-cooling. To the mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with chloroform, washed with brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-2-chloro-1-(5-ethyl-2-thienylmethyl)benzene (4.52 g) as a colorless liquid.

Reference Example 6

3-Bromo-1-(5-n-propyl-2-thienylmethyl)benzene

3-Bromobenzoic acid and 2-n-propylthiophene were used and treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 7

5-Bromo-(5-ethyl-2-thienylmethyl)2-methoxybenzene

(1) A solution of 2-ethylthiophene (3.00 g) in tetrahydrofuran (36 ml) was cooled to 0°C under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.56 M hexane solution, 17.1 ml). The mixture was stirred at the same temperature for 30 minutes, and cooled to -78°C, and thereto was added dropwise a suspension of 5-bromo-2-methoxybenzaldehyde (5.74 g) in tetrahydrofuran (60 ml). The mixture was stirred at the same temperature for 2 hours, warmed to 0°C, and thereto was added a saturated aqueous ammonium chloride solution. The mixture was extracted with

ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 - 85:15) to give 5-bromo-2-methoxyphenyl-5-ethyl-2-thienylmethanol (5.99 g) as a pale yellow syrup. APCI-Mass m/Z 309/311 ($M+H-H_2O$).

(2) The above 5-bromo-2-methoxyphenyl-5-ethyl-2-thienylmethanol was treated in a manner similar to Reference Example 1-(2) to give 5-bromo-(5-ethyl-2-thienylmethyl)-2-methoxybenzene as oil. APCI-Mass m/Z 311/313 (M+H).

Reference Example 8 3-Bromo-1-(5-ethyl-2-thienylmethyl)-4-methoxybenzene

2-Ethylthiophene and 3-bromo-4-methoxybenzaldehyde were used and treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 9

3-Bromo-1-(4-n-propyl-2-thienylmethyl)benzene

(1) 3-n-Propylthiophene and 3-bromobenzaldehyde were used and treated in a manner similar to Reference Example 7 -(1) to give 3-bromophenyl-4-n-propyl-2-thienyl methanol. APCI-Mass m/Z 293/295 ($M+H-H_2O$).

(2) A solution of the above 3-bromophenyl-4-n-propyl-2-thienyl methanol (2.4 g) in acetonitrile (10 ml) was added dropwise to a mixed solution of chlorotrimethylsilane (4.54 ml) and sodium iodide (5.36 g) in acetonitrile (10 ml) at 0°C, over a period of 2 hours. The mixture was further stirred at room temperature for 5 minutes, and cooled again to 0°C. An aqueous solution (10 ml) of sodium hydroxide (1.0 g) was added thereto, and the mixture was stirred at 0 °C for 0.5 hours. The mixture was extracted with ethyl

acetate, washed successively with an aqueous sodium thiosulfate solution, water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 3-bromo-1-(4-n-propyl-2-thienyl)benzene (1.97 g) as colorless oil.

Reference Example 10

5-Bromo-2-chloro-1-(5-n-propyl-2-thienylmethyl)benzene

5-Bromo-2-chlorobenozoic acid and 2-n-propylthiophene were used and treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 11

5-Bromo-2-methoxy-1-(5-n-propyl-2-thienylmethyl)benzene

2-n-Propylthiophene and 5-bromo-2-methoxybenzaldehyde were used and treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 325/327 (M+H).

Reference Example 12

3-Bromo-1-(4-ethyl-2-thienylmethyl)benzene

3-Ethylthiophene and 3-bromobenzaldehyde were used and treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 281/283 (M+H).

Reference Example 13

3-Bromo-1-(4-chloro-5-ethyl-2-thienylmethyl)benzene

(1) To a solution of 5-ethyl-2-thiophenecarboxaldehyde (6.0 g) in N,N-dimethylformamide (60 ml) was added N-chlorosuccinimide (8.57 g), and the mixture was stirred at room temperature for 2 hours, and subsequently stirred under heating at 60°C for 2 hours. N-chlorosuccinimide (4.00 g) was further added thereto, and the mixture was further stirred under

heating at 60°C for 2 hours. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 33:1) to give 4-chloro-5-ethyl-2-thiophenecarboxaldehyde (3.1 g) as colorless oil.

(2) The above 4-chloro-5-ethyl-2-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 1 to give 3-bromo-1-(4-chloro-5-ethyl-2-thienylmethyl)benzene as yellow oil. APCI-Mass m/Z 347/349 (M+H+MeOH).

Reference Example 14

5-Bromo-2-chloro-1-(4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylmethyl)benzene

(1) To a solution of 4-keto-4,5,6,7-tetrahydrothianaphthene (9.83 g) in ethylene glycol (100 ml) were added hydrazine hydrate (10.4 ml) and potassium hydroxide (13.0 g), and the mixture was stirred under argon atmosphere at 190°C for 4 hours. The reaction mixture was cooled to room temperature, and poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 4,5,6,7-tetrahydrothianaphthene (2.75g) as colorless oil.

(2) The above 4,5,6,7-tetrahydrothianaphthene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylmethyl)benzene as a colorless solid. APCI-Mass m/Z 341/343 (M+H).

Reference Example 15

5-Bromo-2-chloro-1-(5-ethyl-4-methyl-2-thienylmethyl)-benzene

(3) 2-Acetyl-3-methylthiophene was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 329/331 (M+H).

Reference Example 16

5-Bromo-2-chloro-1-(2-thieno[3,2-b]thienylmethyl)benzene

(1) 5-Bromo-2-chlorobenzoic acid was treated in a manner similar to Reference Example 4-(2) and (3) to give 5-bromo-2-chlorobenzaldehyde. APCI-Mass m/Z 233/235 (M+H+MeOH-H_2O).

(2) The above 5-bromo-2-chlorobenzaldehyde and thieno[3,2-b]thiophene (see Fuller, L.; Iddon, B.; Smith, K. A. *J. Chem. Soc. Perkin Trans 1* 1997, 3465 - 3470) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(2-thieno[3,2-b]thienylmethyl)benzene as colorless oil. APCI-Mass m/Z 343/345 (M+H).

Reference Example 17

5-Bromo-2-chloro-1-(5-chloro-2-thienylmethyl)benzene

2-Chlorothiophene was treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 18

5-Bromo-2-chloro-1-(5-phenylmethyl-2-thienylmethyl)benzene

2-Benzoylthiophene was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 377/379 (M+H).

Reference Example 19

5-Bromo-2-chloro-1-(5-(2-thienyl)-2-thienylmethyl)benzene

2,2′-Bithiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were used and treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 369/371 (M+H).

Reference Example 20 5-Bromo-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)-2-methylbenzene

(1) To a solution of 2-bromo-5-chlorothiophene (4.11 g), thiophene-2-boronic acid (4.00 g), tetrakis(triphenylphosphine)palladium (0) (1.20 g) and 2M aqueous sodium carbonate solution (31.3 ml) in dimethoxyethane (100 ml) was heated under reflux under argon atmosphere for 2.5 hours. The reaction mixture was cooled, and extracted with ethyl acetate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 2-(5-chloro-2-thienyl)thiophene (3.37 g) as pale yellow oil.

(2) The above 2-(5-chloro-2-thienyl)thiophene and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were used and treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)-2-methylbenzene as a colorless solid. APCI-Mass m/Z 383/385 (M+H).

Reference Example 21

5-Bromo-2-chloro-1-(4-chloro-5-ethyl-2-thienylmethyl)-benzene

2-Acetyl-3-chlorothiophene (see Japanese Unexamined Patent Publication No. 2000-34230) was treated in a manner similar to Reference Example 14 to give the target compound. APCI-Mass m/Z 347/349 (M+H).

Reference Example 22 5-Chloro-4-methylthiophene

The target compound was prepared according to a method described in Japanese Unexamined Patent Publication No. 10-324632.

Reference Example 23

5-Bromo-2-chloro-1-(5-(5-chloro-2-thienyl)-2-thienylmethyl)benzene

2-(5-Chloro-2-thienyl)thiophene and 5-bromo-2-chlorobenzoic acid were treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 24

5-Bromo-2-chloro-1-(5-trifluoromethyl-2-thienylmethyl)-benzene

2-Trifluoromethylthiophene (see Japanese Unexamined Patent Publication No. 2000-34239) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 25

5-Bromo-2-chloro-1-(5-(2-pyridyl)-2-thienylmethyl)benzene

(1) 2-(2-Pyridyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-2-chlorophenyl-5-(2-pyridyl)-2-thienylmethanol as colorless powder. APCI-Mass m/Z 380/382 (M+H).

(2) A solution of the above 5-bromo-2-chlorophenyl-5-(2-pyridyl)-2-thienylmethanol (3.52 g) in trifluoroacetic acid (45 ml) was added to a solution of sodium borohydride (1.75 g) in trifluoroacetic acid (45 ml), and the mixture was stirred at room temperature for 4 hours. Trifluoroacetic acid was evaporated under reduced pressure.

The residue was basified with an aqueous potassium hydroxide solution, and extracted with diethyl ether. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1-4:1) to give 5-bromo-2-chloro-1-(5-(2-pyridyl)-2-thienylmethyl)benzene (2.42 g) as a colorless solid. APCI-Mass m/Z 364/366 (M+H).

Reference Example 26

5-Bromo-1-(5-chloro-2-thienylmethyl)-2-phenylbenzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) and 2-chlorothiophene were treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-chloro-2-thienylmethyl)-2-iodobenzene as colorless oil.

(2) To a solution of the above 5-bromo-1-(5-chloro-2-thienylmethyl)-2-iodobenzene (1.0 g) in dimethoxyethane (10 ml) were added phenylboronic acid (310 mg), bis(triphenylphosphine)palladium (II) dichloride (85 mg) and 2M aqueous sodium carbonate solution (3.8 ml), and the mixture was stirred at 50°C overnight. Added thereto was a saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 5-bromo-1-(5-chloro-2-thienylmethyl)-2-phenylbenzene (683 mg) as oil.

Reference Example 27 2-Chlorothieno[3,2-b]thiophene

(1) A solution of thieno[3,2-b]thiophene (see Fuller, L.; Iddon, B.; Smith, K. A. *J. Chem. Soc. Perkin Trans 1* 1997, 3465 - 3470) (1.27 g) in tetrahydrofuran (30 ml) was cooled to -78°C

under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 5.70 ml). The mixture was stirred at 0°C for 30 minutes, and cooled again to -78°C. Added thereto was a solution of hexachloroethane (2.14 g) in tetrahydrofuran (5 ml). The mixture was stirred at the same temperature for one hour, and warmed to 0°C. Added thereto was a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give 2-Chlorothieno[3,2-b]thiophene (1.19 g) as a solid.

Reference Example 28

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methoxybenzene

Thianaphthene was treated in a manner similar to Reference Example 7 to give the target compound. ESI-Mass m/Z 331/333(M-H).

Reference Example 29

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-chlorobenzene

Thianaphthene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 30

3-Bromo-1-(5-methylbenzo[b]thiophen-2-ylmethyl)benzene

5-Methylbenzo[b]thiophene and 3-bromobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 31

3-Bromo-1-(6-fluorobenzo[b]thiophen-2-ylmethyl)benzene

(1) To a solution of 2,4-difluorobenzaldehyde (5.0 g) in

dimethylsulfoxide (100 ml) were added methyl thioglycolate (3.45 ml) and triethylamine (10 ml), and the mixture was stirred at 80°C overnight. The reaction mixture was poured into ice-cold water. The mixture was extracted with ethyl acetate, washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 7:1) to give 6-fluoro-2-methoxycarbonylbenzo[b]thiophene (1.32 g) as colorless powder. GC-EI-Mass m/Z 210 (M).

(2) The above 6-fluoro-2-methoxycarbonylbenzo[b]thiophene was treated in a manner similar to Reference Example 4-(1) to give 6-fluorobenzo[b]thiophen-2-ylcarboxylic acid as colorless powder. ESI-Mass m/Z 195 (M-H).

(3) The above 6-fluorobenzo[b]thiophen-2-ylcarboxylic acid was treated in a manner similar to Reference Example 4-(2) to give 6-fluoro-2-(N-methoxy-N-methylcarbamoyl)benzo[b]thiophene as colorless powder. APCI-Mass m/Z 240 (M+H).

(4) A solution of 1,3-dibromobenzene (493 mg) in tetrahydrofuran (10 ml) was cooled to -78°C under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 0.86 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of the above 6-fluoro-2-(N-methoxy-N-methylcarbamoyl)benzo[b]thiophene (500 mg) in tetrahydrofuran (3 ml). The mixture was warmed to room temperature, and added thereto was a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 95:5-85:15) to give 3-bromophenyl

6-fluorobenzo[b]thiophen-2-yl ketone (479 mg) as a pale yellow solid. APCI-Mass m/Z 335/337 ($M+NH_4$).

(5) The above 3-bromophenyl 6-fluorobenzo[b]thiophen-2-yl ketone was treated in a manner similar to Reference Example 5-(2) to give 3-bromo-1-(6-fluorobenzo[b]thiophen-2-ylmethyl)benzene as a colorless solid.

Reference Example 32

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-fluorobenzene

Thianaphthene and 3-bromo-4-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 33

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethoxybenzene

Thianaphthene and 5-bromo-2-ethoxybenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 34

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-fluorobenzene

Thianaphthene and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 35

2-(Benzo[b]thiophen-2-ylmethyl)-4-bromo-1-methoxy-naphthalene

2,4-Dibromo-1-methoxynaphthalene (see J. Clayden, et al. *Org. Lett.*, 5, (2003) 831) and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 36

3-Bromo-1-(5-trifluoromethylbenzo[b]thiophen-2-ylmethyl)benzene

5-Trifluoromethylbenzo[b]thiophen-2-ylcarboxylic acid was treated in a manner similar to Reference Example 31- (3), (4), and (5) to give the target compound.

Reference Example 37

3-Bromo-1-(3-methylbenzo[b]thiophen-2-ylmethyl)benzene

3-Methylbenzo[b]thiophene-2-carboxaldehyde was treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 38

3-Bromo-1-(5-fluorobenzo[b]thiophen-2-ylmethyl)benzene

2,5-Difluorobenzaldehyde was treated in a manner similar to Reference Example 31 to give the target compound.

Reference Example 39

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-methylbenzene

(1) 3-Bromo-4-methylbenzoic acid was treated in a manner similar to Reference Example 4-(2) and (3) to give 3-bromo-4-methylbenzaldehyde as colorless crystals.

APCI-Mass m/Z 213/215 (M+H+MeOH).

(2) The above 3-bromo-4-methylbenzaldehyde and thianaphthene were treated in a manner similar to Reference Example 7 to give (Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-methylbenzene as a colorless solid.

Reference Example 40

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-5-methylbenzene

3,5-Dibromotoluene and benzo[b]thiophene-2-carboxaldehyde

were treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 41

5-Bromo-2-chloro-1-(5-methylbenzo[b]thiophen-2-ylmethyl)benzene

5-Methylbenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16- (1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 42

5-Bromo-2-chloro-1-(7-methylbenzo[b]thiophen-2-ylmethyl)benzene

7-Methylbenzo[b]thiophene (see Tilak, B. D. *Tetrahedron* 9 (1960) 76-95)and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 43

5-Bromo-2-chloro-1-(5-chlorobenzo[b]thiophen-2-ylmethyl)benzene

5-Chlorobenzo[b]thiophene (see Tilak, B. D. *Tetrahedron* 9 (1960) 76-95)and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 44

5-Bromo-2-chloro-1-(5,7-dimethylbenzo[b]thiophen-2-ylmethyl)benzene

5,7-Dimethylbenzo[b]thiophene (see Yoshimura, Y. et al., *J. Med. Chem.* 43 (2000) 2929-2937) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner

similar to Reference Example 7 to give the target compound.

Reference Example 45

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methylbenezene

(1) A solution of thianaphthene (543 mg) in diethyl ether (20 ml) was cooled to 0°C under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 1.74 ml). The reaction mixture was stirred at the same temperature for 3 hours. The reaction mixture was added dropwise to a solution of N-methoxy-N-methyl-5-bromo-2-methylbenzamide (1.15 g) obtained in Reference Example 4-(2) in diethyl ether (10 ml) cooled to -78°C. The mixture was warmed to room temperature and stirred for one hour. Added thereto was a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-95:5) to give 5-bromo2-methylphenyl benzo[b]thiophen-2-yl ketone (995 mg) as a pale yellow syrup. APCI-Mass m/Z 331/333 (M+H).

(2) The above 5-bromo2-methylphenyl benzo[b]thiophen-2-yl ketone was treated in a manner similar to Reference Example 5-(2) to give 1-(benzo[b]thiophen-2-ylmethyl)-5-bromo-2-methylbenezene as colorless oil.

Reference Example 46

5-Bromo-2-chloro-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)-benzene

6-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 47

5-Bromo-2-chloro-1-(6-chlorobenzo[b]thiophen-2-ylmethyl)-benzene

(1) 4-Chloro-2-fluorobenzaldehyde was treated in a manner similar to Reference Example 31-(1) and (2) to give 6-chlorobenzo[b]thiophen-2-ylcarboxylic acid as colorless crystals. ESI-Mass m/Z 211/213 (M-H).

(2) A solution of the above 6-chlorobenzo[b]thiophen-2-ylcarboxylic acid (3.0 g) and copper powder (1.2 g) in quinoline (20 ml) was stirred at 210°C for 40 minutes. The mixture was cooled to room temperature and diluted with diethyl ether, and insoluble materials were filtered off. The filtrate was washed successively with 10% aqueous hydrochloric acid solution and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 6-chlorobenzo[b]thiophene (1.79 g) as colorless crystals.

(3) The above 6-chlorobenzo[b]thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 7 to give. 5-bromo-2-chloro-1-(6-chlorobenzo[b]thiophen-2-ylmethyl)benzene as colorless crystals.

Reference Example 48

5-Bromo-2-chloro-1-(6-trifluoromethylbenzo[b]thiophen-2-ylmethyl)benzene

2-Fluoro-4-trifluoromethylbenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 49

1-Benzo[b]thiophen-2-ylmethyl)-3-bromo-4-chlorobenzene

3-Bromo-4-chlorobenzoic acid was treated in a manner similar to Reference Example 39 to give the target compound.

Reference Example 50

5-Bromo-2-chloro-1-(6-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

2,4-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 51

5-Bromo-2-fluoro-1-(6-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

6-Fluorobenzo[b]thiophene produced in the preparation process of Reference Example 50 and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 52

1-(Benzo[b]thiophen-2-ylmethyl)-3-bromo-5-chlorobenzene

1-Chloro-3,5-dibromobenzene and benzo[b]thiophene-2-carboxaldehyde were treated in a manner similar to Reference Example 1 to give the target compound.

Reference Example 53

5-Bromo-2-chloro-1-(7-methoxybenzo[b]thiophen-2-ylmethyl)-benzene

7-Methoxybenzo[b]thiophene (see WO 02/094262) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 367/369 (M+H).

Reference Example 54

5-Bromo-2-chloro-1-(5-methoxybenzo[b]thiophen-2-ylmethyl)-benzene

5-Methoxybenzo[b]thiophene (see WO 97/25033) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 367/369 (M+H).

Reference Example 55

5-Bromo-2-chloro-1-(5-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

2,5-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 56

5-Bromo-2-chloro-1-(7-fluoro-6-methylbenzo[b]thiophen-2-ylmethyl)benzene

2,3-Difluoro-4-methylbenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound. APCI-Mass m/Z 369/371 (M+H).

Reference Example 57

5-Bromo-2-chloro-1-(4-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

2,6-Difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 58

5-Bromo-2-chloro-1-(7-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

2,3-difluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 59

5-Bromo-2-chloro-1-(4-chlorobenzo[b]thiophen-2-ylmethyl)-benzene

2-Chloro-6-fluorobenzaldehyde was treated in a manner similar to Reference Example 47 to give the target compound.

Reference Example 60

5-Bromo-2-fluoro-1-(5-fluorobenzo[b]thiophen-2-ylmethyl)-benzene

5-Fluorobenzo[b]thiophene produced in the preparation process of Reference Example 55 and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 61

3-Bromo-2-chloro-1-(benzo[b]thiophen-2-ylmethyl)benzene

(1) 3-Bromo-2-chlorobenzoic acid (see Frederic Gohier et al., *J. Org. Chem.* (2003) 68 2030-2033.) was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-3-bromo-2-chlorobenzamide as oil.

APCI-Mass m/Z 278/280/282 (M+H).

(2) The above N-methoxy-N-methyl-3-bromo-2-chlorobenzamide was treated in a manner similar to Reference Example 45 to give 3-bromo-2-chloro-1-(benzo[b]thiophen-2-ylmethyl)benzene as a colorless solid.

Reference Example 62

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethylbenzene

(1) To a solution of 2-ethylbenzoic acid (10.0 g) in dichloromethane (50 ml) were added oxalyl chloride (7.0 ml) and N,N-dimethylformamide (3 drops) and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure to give a corresponding acid chloride. The

acid chloride was dissolved in methanol (60 ml) and the mixture was stirred at room temperature for 3 hours, and then, the solvent was evaporated under reduced pressure. The residue was dissolved in diethyl ether, and washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give methyl 2-ethylbenzoate, which was used in the subsequent step without further purification.

(2) The above methyl 2-ethylbenzoate was mixed with molecular sieve 13X (powder, 70 g), and while stirring the mixture, bromine (5.2 ml) was added dropwise thereto at 80°C. The mixture was further stirred at the same temperature for 1.5 hours. The mixture was cooled to room temperature, and added thereto were potassium carbonate (7.4 g), water (70 ml) and methanol (350 ml), and the mixture was stirred for 8 hours. Insoluble materials were filtered off, and suspended in a mixed solution of methanol (500 ml) - water (500 ml), and the mixture was stirred at room temperature overnight. Insoluble materials were filtered off and the filtrate was combined with the previously obtained filtrate, and the solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was distilled under reduced pressure, to give methyl 5-bromo-2-ethylbenzoate (2.44 g). APCI-Mass m/Z 260/262 ($M+NH_4$).

(3) The above methyl 5-bromo-2-ethylbenzoate was treated in a manner similar to Reference Example 4-(1) and (2) to give N-methoxy-N-methyl-5-bromo-2-ethylbenzamide as colorless oil. APCI-Mass m/Z 272/274 (M+H).

(4) The above N-methoxy-N-methyl-5-bromo-2-ethylbenzamide and thianaphthene were treated in a manner similar to Reference Example 45 to give

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-ethylbenzene as oil.

Reference Example 63

1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-trifluoromethylbenzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-5-bromo-2-iodobenzamide as a pale yellow solid. APCI-Mass m/Z 370/372 (M+H).

(2) To a solution of the above N-methoxy-N-methyl-5-bromo-2-iodobenzamide (2.67 g) in N-methyl-2-pyrrolidinone (12 ml) were added copper (I) bromide (124 mg) and methyl fluorosulfonyl(difluoro)acetate (1.34 ml), and the mixture was stirred under heating for 1.5 hours. The reaction mixture was cooled to room temperature, and then, a diluted aqueous ammonia was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 100:0 - 85:15) to give N-methoxy-N-methyl-5-bromo-2-trifluoromethylbenzamide (1.59 g) as colorless oil. APCI-Mass m/Z 312/314 (M+H).

(3) The above N-methoxy-N-methyl-5-bromo-2-trifluoromethylbenzamide and thianaphthene were treated in a manner similar to Reference Example 45 to give 1-(Benzo[b]thiophen-2-ylmethyl)-5-bromo-2-trifluoromethylbenzene as a colorless solid. ESI-Mass m/Z 369/371 (M-H).

Reference Example 64

5-Bromo-2-chloro-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene was treated in a manner similar to Reference Example 5 to give the target compound. APCI-Mass m/Z 363/365 (M+H).

Reference Example 65

5-Bromo-2-chloro-1-(5-(4-methylphenyl)-2-thienylmethyl)-benzene

(1) 2-Iodothiophene and 4-methylphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(4-methylphenyl)thiophene as colorless crystals. APCI-Mass m/Z 175 (M+H).

(2) The above 2-(4-methylphenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-methylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 377/379 (M+H).

Reference Example 66

5-Bromo-2-chloro-1-(5-(2-fluorophenyl)-2-thienylmethyl)-benzene

(1) 2-Fluorobromobenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(2-fluorophenyl)thiophene as a colorless liquid.

(2) The above 2-(2-fluorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(2-fluorophenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 381/383 (M+H).

Reference Example 67

5-Bromo-2-chloro-1-(5-(4-fluorophenyl)-2-thienylmethyl)-benzene

(1) 2-Iodothiophene and 4-fluorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give

2-(4-fluorophenyl)thiophene as colorless powder.

(2) The above 2-(4-fluorophenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-fluorophenyl)-2-thienylmethyl)benzene as colorless powder.

Reference Example 68

5-Bromo-2-chloro-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)-benzene

(1) 2-Bromothiophene and 4-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-ethoxyphenyl)thiophene as a colorless solid. APCI-Mass m/Z 205 (M+H).

(2) The above 2-(4-ethoxyphenyl)thiophene was treated in a manner similar to Reference Example 5 to give 5-bromo-2-chloro-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)benzene as a colorless solid. APCI-Mass m/Z 407/409 (M+H).

Reference Example 69

5-Bromo-2-chloro-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)-benzene

(1) 2-Bromothiophene and 3-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-ethoxyphenyl)thiophene as colorless oil. APCI-Mass m/Z 205 (M+H).

(2) The above 2-(3-ethoxyphenyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)benzene as colorless oil. APCI-Mass m/Z 407/409 (M+H).

Reference Example 70

5-Bromo-2-chloro-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)-benzene

(1) 2-Iodothiophene and 2-ethoxyphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(2-ethoxyphenyl)thiophene as a pale yellow solid.

(2) The above 2-(2-ethoxyphenyl)thiophene and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give 5-bromo-2-chloro-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)benzene as colorless oil. APCI-Mass m/Z 407/409 (M+H).

Reference Example 71

5-Bromo-2-fluoro-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 347/349 (M+H).

Reference Example 72

5-Bromo-1-(5-(4-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(4-Ethoxyphenyl)thiophene obtained in Reference Example 68-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

Reference Example 73

5-Bromo-1-(5-(2-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(2-Ethoxyphenyl)thiophene obtained in Reference Example 70-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 9 to give the target

compound. APCI-Mass m/Z 391/393 (M+H).

Reference Example 74
5-Bromo-2-fluoro-1-(5-(2-fluorophenyl)-2-thienylmethyl)-benzene

2-(2-Fluorophenyl)thiophene obtained in Reference Example 66-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 365/367 (M+H).

Reference Example 75
5-Bromo-2-chloro-1-(5-(3-fluorophenyl)-2-thienylmethyl)-benzene

(1) 2-Iodothiophene and 3-fluorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-fluorophenyl)thiophene as oil.

(2) The above 2-(3-fluoropheny)thiophene was treated in a manner similar to Reference Example 5 to give the target compound as powder.

Reference Example 76 5-Bromo-1-(5-(3-ethoxyphenyl)-2-thienylmethyl)-2-fluorobenzene

2-(3-Ethoxyphenyl)thiophene obtained in Reference Example 69-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 391/393 (M+H).

Reference Example 77
5-Bromo-2-fluoro-1-(5-(3-fluorophenyl)-2-thienylmethyl)-benzene

2-(3-Fluorophenyl)thiophene obtained in Reference Example 75-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target

compound.

Reference Example 78

5-Bromo-2-fluoro-1-(5-(4-fluorophenyl)-2-thienylmethyl)-benzene

2-(4-Fluorophenyl)thiophene obtained in Reference Example 67-(1) and 5-bromo-2-fluorobenzaldehyde were treated in a manner similar to Reference Example 7 to give the target compound.

Reference Example 79

5-Bromo-2-methyl-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound. APCI-Mass m/Z 343/345 (M+H).

Reference Example 80

5-Bromo-1-(5-(3-fluorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(3-Fluorophenyl)thiophene obtained in Reference Example 75-(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 81

5-Bromo-1-(5-(4-fluorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(4-Fluorophenyl)thiophene obtained in Reference Example 67-(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound.

Reference Example 82

5-Bromo-2-methoxy-1-(5-phenyl-2-thienylmethyl)benzene

2-Phenylthiophene was treated in a manner similar to Reference Example 7 to give the target compound. APCI-Mass m/Z 359/361 (M+H).

Reference Example 83

5-Bromo-2-methyl-1-(5-(3-methylphenyl)-2-thienylmethyl)-benzene

(1) 2-Bromothiophene and 3-methylphenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-methylphenyl)thiophene as colorless oil.

(2) The above 2-(3-methylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 357/359 (M+H).

Reference Example 84

5-Bromo-2-chloro-1-(5-(3-methylphenyl)-2-thienylmethyl)-benzene

2-(3-Methylphenyl)thiophene obtained in Reference Example 83-(1) and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 9 to give the target compound. APCI-Mass m/Z 377/379/381 (M+H).

Reference Example 85

5-Bromo-2-chloro-1-(5-(3-chlorophenyl)-2-thienylmethyl)-benzene

(1) 2-Bromothiophene and 3-chlorophenylboronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-chlorophenyl)thiophene as colorless oil.

(2) The above 2-(3-chlorophenyl)thiophene was treated in a

manner similar to Reference Example 5 to give the target compound as colorless oil.

Reference Example 86

5-Bromo-1-(5-(3-chlorophenyl)-2-thienylmethyl)-2-methylbenzene

2-(3-Chlorophenyl)thiophene obtained in Reference Example 85-(1) and 5-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give the target compound as colorless oil.

Reference Example 87

5-Bromo-1-(5-(3-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene

(1) 3-Methoxybromobenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 26-(2) to give 2-(3-methoxyphenyl)thiophene as a yellow liquid. APCI-Mass m/Z 191 (M+H).

(2) The above 2-(3-methoxyphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give the target compound as yellow oil. APCI-Mass m/Z 373/375 (M+H).

Reference Example 88

4-Bromo-2-(4-ethylphenylmethyl)-2H-isoquinolin-1-one

4-Bromo-2H-isoquiolin-1-one (see EP0355750) was treated in a manner similar to Reference Example 2 to give the target compound. APCI-Mass m/Z 342/344 (M+H).

Reference Example 89

4-Bromo-2-(4-ethylphenylmethyl)-8-methyl-2H-isoquinolin-1-one

(1) To a solution of 8-methyl-2H-isoquiolin-1-one (1.15 g) in

dichloromethane (20 ml) was added dropwise a solution of bromine (1.26 g) in dichloromethane (4 ml) at room temperature. The mixture was stirred at the same temperature for one hour, and the solvent was evaporated under reduced pressure. The residue was crystallized from ether to give 4-bromo-8-methyl-2H-isoquinolin-1-one (1.86 g) as colorless crystals. APCI-Mass m/Z 238/240 (M+H).

(2) The above 4-bromo-8-methyl-2H-isoquinolin-1-one was treated in a manner similar to Reference Example 2 to give the target compound as colorless crystals. APCI-Mass m/Z 356/358M+H).

Reference Example 90

4-Bromo-2-(4-ethylphenylmethyl)thiophene

(1) A solution of 4-bromo-2-thiophenecarboxaldehyde (4.78 g) in tetrahydrofuran (40 ml) was cooled to 0°C under argon atmosphere, and thereto was added dropwise 4-ethylphenylmagnesium bromide (0.5 M tetrahydrofuran solution, 50 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 97:3 - 84:16) to give 4-bromo-2-thienyl-4-ethylphenylmethanol (5.37 g) as colorless oil. APCI-Mass m/Z 279/281 ($M+H-H_2O$).

(2) The above 4-bromo-2-thienyl-4-ethylphenylmethanol was treated in a manner similar to Reference Example 1-(2) to give the target compound as colorless oil.

Reference Example 91

5-Bromo-2-(4-ethylphenylmethyl)thiophene

5-Bromo-2-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 90 to give the target compound. ESI-Mass m/Z 279/281 (M-H).

Reference Example 92

3-Bromo-2-(4-ethylphenylmethyl)thiophene

(1) 2,3-Dibromothiophene and 4-ethylbenzaldehyde were treated in a manner similar to Reference Example 1-(1) to give 3-bromo-2-thienyl-4-ethylphenylmethanol as yellow oil. APCI-Mass m/Z 279/281 ($M+H-H_2O$).

(2) A solution of the above 3-bromo-2-thienyl-4-ethylphenylmethanol (12.4 g) in diethyl ether (10 ml) was added dropwise into a suspension of lithium aluminum hydride (2.6 g) and aluminum chloride (9.0 g) in diethyl ether (35 ml) at 0°C. Subsequently, the mixture was stirred at room temperature overnight, and then poured onto ice. The mixture was extracted with diethyl ether, washed with a saturated aqueous sodium hydrogen carbonate solution, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give 3-bromo-2-(4-ethylphenylmethyl)thiophene (8.77 g) as colorless oil. APCI-Mass m/Z 279/281 (M+H).

Reference Example 93

5-Bromo-3-(4-ethylphenylmethyl)thiophene

5-Bromo-3-thiophenecarboxaldehyde (see Amishiro, N. et al., *Chem. Pharm. Bull.* 47 (1999) 1393-1403.) was treated in a manner similar to Reference Example 90 to give the target compound.

Reference Example 94

5-Bromo-2-chloro-3-(4-ethylphenylmethyl)thiophene

(1) 5-Bromo-2-chloro-3-thiophenecarboxylic acid (see Japanese Unexamined Patent Publication No. 10-324632) was treated in a manner similar to Reference Example 4-(2) and (3) to give 5-bromo-2-chloro-3-thiophenecarboxaldehyde as pale yellow oil. APCI-Mass m/Z 239/241/243 (M+H+MeOH-H_2O).

(2) The above 5-bromo-2-chloro-3-thiophenecarboxaldehyde was treated in a manner similar to Reference Example 90 to give the target compound as colorless oil.

Reference Example 95

5-Bromo-3-chloro-2-(4-ethylphenylmethyl)thiophene

(1) A solution of diisopropylamine (6.8 ml) in tetrahydrofuran (75 ml) was cooled to -78°C under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.59 M hexane solution, 30.5 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of 3-chloro-2-thiophenecarboxylic acid (3.92 g) in tetrahydrofuran (40 ml). The mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise 1,2-dibromo-1,1,2,2-tetrafluoroethane (6.0 ml). The mixture was stirred at the same temperature for one hour, and then, warmed to room temperature. The mixture was poured into a diluted aqueous hydrochloric acid solution, and the solution was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was crystallized from a mixed solvent of diisopropyl ether and hexane to give 5-bromo-3-chloro-2-thiophenecarboxylic acid (3.79 g) as a yellow solid. ESI-Mass m/Z 239/241 (M-H).

(2) The above 5-bromo-3-chloro-2-thiophenecarboxylic acid was treated in a manner similar to Reference Example 94 to give 5-bromo-3-chloro-2-(4-ethylphenylmethyl)thiophene as

by silica gel column chromatography (hexane:ethyl acetate = 100:0 - 90:10) to give 5-phenylthiazole (1.50 g) as a pale yellow solid. APCI-Mass m/Z 162 (M+H).

(2) The above 5-phenylthiazole and 5-bromo-2-chlorobenzaldehyde obtained in Reference Example 16-(1) were treated in a manner similar to Reference Example 100 to give 5-bromo-2-chloro-1-(5-phenyl-2-thiazolylmethyl)benzene as a yellow solid. APCI-Mass m/Z 364/366 (M+H).

Reference Example 103

3-(4-Ethylphenylmethyl)-2,4-pentanedione

A suspension of sodium iodide (15.0g) in acetonitrile (100ml) was cooled to 0°C under argon atmosphere, and thereto were added dropwise chlorotrimethylsilane (12.7ml), 2,4-pentanedione (2.05ml) and 4-ethylbenzaldehide (2.68g), successively. The reaction mixture was stirred at room temperature for 17 hours, and further stirred at 60°C for 10 hours. The reaction mixture was cooled to room temperature and poured into an aqueous sodium thiosulfate solution. The mixture was extracted with diethyl ether, and the extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to give 3-(4-ethylphenylmehyl)-2,4-pentanedione (2.72g) as pale yellow oil. APCI-Mass m/Z 219 (M+H).

Reference Example 104 Tri-n-butyl(4-ethylphenyl)tin

To a solution of magnesium (896 mg) in tetrahydrofuran (20 ml) was added dibromoethan (0.1 ml), and the mixture was stirred at room temperature for 15 minutes. Thereto was added dropwise a solution of 1-bromo-4-ethylbenzene (5.7 g) in tetrahydrofuran (20 ml), and subsequently, the mixture was stirred at room

temperature for one hour. The reaction mixture was cooled to -78°C, and thereto was added dropwise tributyltin chloride (9.49 g). The mixture was stirred at the same temperature for 30 minutes, and then at room temperature for one hour. To the reaction mixture were added 10% aqueous potassium fluoride solution and ethyl acetate, and the mixture was stirred at room temperature for 30 minutes. Insoluble materials were filtered off. The organic layer of the filtrate was washed with water and brine successively, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by alumina column chromatography (hexane) to give the desired tri-n-butyl(4-ethylphenyl)tin (10.7 g) as colorless oil. EI-Mass m/Z 337 (M-Bu).

Reference Example 105 4-(4-Ethylphenylmethyl)pyrazole

(1) A mixed solution of 4-ethylbenzyl bromide (10.0 g), malononitrile (6.64 g), potassium carbonate (6.94 g) and tetra-n-butylammonium bromide (648 mg) in toluene (100 ml) was agitated at room temperature for 17 hours. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate twice. The extract was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 6:1) to give 2-(4-ethylphenylmethyl)malononitrile (3.28 g) as a colorless solid.

(2) A solution of the above 2-(4-ethylphenylmethyl)malononitrile (1.30 g) and hydrazine hydrate (0.86 ml) in ethanol (35 ml) was heated under reflux for 4 hours. Hydrazine hydrate (0.43 ml) was further added thereto and the mixture was further heated under reflux for 4 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue

was crystallized from ethyl acetate-diethyl ether to give 3,5-diamino-4-(4-ethylphenylmethyl)pyrazole (2.63 g) as pale pink powder. APCI-Mass m/Z 217 (M+H).

(3) The above 3,5-diamino-4-(4-ethylphenylmethyl)pyrazole (1.30 g) was added to 50% aqueous phosphoric acid solution (19 ml), and further added thereto was water (10 ml). The mixture was cooled to 0°C, and thereto was added dropwise an aqueous solution (4 ml) of sodium nitrite (912 mg). The mixture was stirred at the same temperature for 30 minutes, and further stirred at room temperature for 4 hours. The reaction mixture was cooled again to 0°C, 10% aqueous sodium hydroxide solution was added thereto to adjust pH of the reaction mixture to 7. The mixture was extracted with ethyl acetate, washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 - 90:10) to give the desired 4-(4-ethylphenylmethyl)pyrazole (414 mg) as a pale brown semisolid. APCI-Mass m/Z 187 (M+H).

Reference Example 106

3-(4-Ethylphenylmethyl)-5-methyl-1H-pyrazole

(1) 4-Ethylphenylacetic acid (3.0 g) (see Japanese Unexamined Patent Publication 63-233975) was dissolved in dichloromethane (15 ml), and thereto were added oxalyl chloride (6.0 ml) and N,N-dimethylformamide (one drop). The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was evaporated under reduced pressure, and the residue was subjected to azeotropic distillation with toluene to give a crude 4-ethylphenylacetyl chloride, which was used in the subsequent step without further purification.

(2) A suspension of magnesium chloride (1.74 g) in dichloromethane (30 ml) was cooled to 0°C, and thereto were

added t-butyl acetoacetate (3.03 ml) and pyridine (2.96 ml), and successively was added a solution of the above 4-ethylphenylacetyl chloride in dichloromethane (30 ml). The mixture was stirred at the same temperature for 2.5 hours, and an aqueous citric acid solution was added thereto. The mixture was extracted with chloroform. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate =15:1) to give t-butyl 2-acetyl-4-(4-ethylphenyl)-3-oxobutyrate (4.75 g) as pale yellow oil. APCI-Mass m/Z 322 ($M+NH_4$).

(3) A solution of the above t-butyl 2-acetyl-4-(4-ethylphenyl)-3-oxobutyrate in trifluoroacetic acid (60 ml) was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate, and the mixture was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to give 1-(4-ethylphenyl)-4-hydroxy-3-penten-2-one (4.00 g) as yellow oil. APCI-Mass m/Z 205 (M+H).

(4) A solution of the above 1-(4-ethylphenyl)-4-hydroxy-3-penten-2-one (3.98 g) and hydrazine hydrate (4.0 ml) in toluene (20 ml) was stirred under heating at 100°C for 1.5 hours. The reaction mixture was cooled to room temperature, and washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:ethyl acetate =2:1) to give 3-(4-ethylphenylmethyl)-5-methyl-1H-pyrazole (3.12 g) as yellow oil. APCI-Mass m/Z 201 (M+H).

Reference Example 107

3-(4-Ethylphenylmethyl)-6-hydroxypyridine

(1) To a solution of 6-chloronicotinoyl chloride (10.0 g) and N,O-dimethylhydroxyamine hydrochloride (6.65 g) in dichloromethane (200 ml) was added dropwise triethylamine (17.2 g) at 0°C. Subsequently the mixture was stirred at room temperature overnight. The mixture was washed successively with water, 5% aqueous citric acid solution, water and brine, and then, dried over sodium sulfate. The solvent was evaporated under reduced pressure to give N-methoxy-N-methyl-6-chloronicotinamide (11.73 g) as pale yellow oil. APCI-Mass m/Z 201/203 (M+H).

(2) A solution of the N-methoxy-N-methyl-6-chloronicotineamide (4.2 g) in tetrahydrofuran (40 ml) was cooled to 0°C, and thereto was added dropwise 4-ethylphenylmagnesium bromide (0.5 M tetrahydrofuran solution, 55 ml). The mixture was stirred at 0°C for 4 hours, and then at the room temperature for 10 minutes. The reaction mixture was cooled again to 0°C, and added thereto was 10% aqueous hydrochloric acid solution. The mixture was extracted with ethyl acetate, and washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 20:1) to give 6-chloro-3-pyridyl 4-ethylphenyl ketone (3.68 g) as colorless crystals. APCI-Mass m/Z 246/248 (M+H).

(3) The above 6-chloro-3-pyridyl 4-ethylphenyl ketone (1.68 g) was dissolved in N-methyl-2-pyrrolidinone (20 ml), and thereto were added benzylalcohol (815 ml) and 60% sodium hydride (275 mg). The mixture was stirred at room temperature for 6 hours, and then at 90°C for one hour. The reaction mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethyl acetate. The extract was

washed with water and subsequently with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 - 95:5) to give 6-benzyloxy-3-pyridyl 4-ethylphenyl ketone (1.68 g) as colorless oil. APCI-Mass m/Z 318 (M+H).

(4) The above 6-benzyloxy-3-pyridyl 4-ethylphenyl ketone (865 mg) was dissolved in ethylene glycol (8.5 ml), and thereto were added hydrazine hydrate (0.44 ml) and potassium hydroxide (550 mg). The mixture was stirred under heating at 190°C for 8 hours. The reaction mixture was cooled to room temperature, and water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water three times, and subsequently with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 - 0:100) to give the desired 3-(4-ethylphenylmethyl)-6-hydoroxypyridine (256 mg) as colorless powder. APCI-Mass m/Z 214 (M+H).

Reference Example 108

3-(4-Ethylphenylmethyl)-2-hydroxypyridine

(1) 2-Chloronicotinoyl chloride was treated in a manner similar to Reference Example 107-(1), (2) and (3) to give 2-benzyloxy-3-pyridyl 4-ethylphenyl ketone as colorless oil. APCI-Mass m/Z 318 (M+H).

(2) The above 2-benzyloxy-3-pyridyl 4-ethylphenyl ketone (1.69 g) was dissolved in ethanol (15 ml), and thereto was added sodium borohydride (403 mg), and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed with water and successively with brine,

and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give crude 2-benzyloxy-3-pyridyl-4-ethylphenylmethanol as colorless oil, which was used in the subsequent step without further purification.

(3) The above 2-benzyloxy-3-pyridyl-4-ethylphenylmethanol was dissolved in methanol (10 ml), and thereto were added concentrated hydrochloric acid (1.0 ml) and 10% palladium-carbon (500 mg). The mixture was stirred at room temperature for 15 hours under hydrogen atmosphere under normal pressure. Insoluble materials were filtered off, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with water and successively with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 - 97:3) to give the desired 3-(4-ethylphenylmethyl)-2-hydoroxypyridine (307 mg) as a pale brown solid. APCI-Mass m/Z 214 (M+H).

Reference Example 109 3-(4-Ethylphenylmethyl)-1H-indole

(1) To a solution of indole (6.00 g) in methanol (60 ml) were added sodium hydroxide (2.25 g) and 4-ethylbenzaldehyde (7.56 g), and the mixture was stirred at room temperature for 3 days under argon atmosphere. Added thereto was water, and methanol was evaporated under reduced pressure. The residue was extracted with diethyl ether, and the extract was washed with water, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 98:2 - 70:30) to give 4-ethylphenyl-(1H-indol-3-yl)methanol (2.10 g) as a colorless solid. APCI-Mass m/Z 234 (M+H-H_2O).

(2) The above 4-ethylphenyl-(1H-indol-3-yl)methanol was

treated in a manner similar to Reference Example 1-(2) to give the desired 3-(4-ethylphenylmethyl)-1H-indole as colorless crystals. APCI-Mass m/Z 236 (M+H).

Reference Example 110 3-(4-Ethylphenylmethyl)-1H-indazole

(1) A mixture of zinc powder (712 mg) and dibromoethane (0.04 ml) in N,N-dimethylformamide (2.5 ml) were stirred under heating at 70°C for 10 minutes under argon atmosphere. The reaction mixture was cooled to room temperature, and chlorotrimethylsilane (0.04 ml) was added thereto, and the mixture was stirred at room temperature for 30 minutes. To the activated zinc solution was added dropwise a solution of 4-ethylbenzyl bromide (1.74 g) in N,N-dimethylformamide (10 ml) at 0°C over a period of 2 hours. Subsequently, the mixture was stirred at 0°C for 2 hours, to prepare a solution of 4-ethylbenzylzinc bromide in N,N-dimethylformamide, which was used in the subsequent step without further purification.

(2) A solution of tris(dibenzylideneacetone)dipalladium (0) (167 mg) and tri(2-furyl)phosphine (135 mg) in tetrahydrofuran (20 ml) was stirred at room temperature for 5 minutes under argon atmosphere. Thereto were added 1-t-butoxycarbonyl-3-iodo-1H-indazole (2.0 g) and the above 4-ethylbenzylzinc bromide (N,N-dimethylformamide solution) at 0°C, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into water, and the mixture was extracted with diethyl ether. The extract was washed with water and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 - 92:8) to give 1-t-butoxycarbonyl-3-(4-ethylphenylmethyl)-1H-indazole (1.37 g) as colorless oil. APCI-Mass m/Z 337 (M+H).

(3) The above

1-t-butoxycarbonyl-3-(4-ethylphenylmethyl)-1H-indazole (1.35 g) was dissolved in methanol (15 ml), and added thereto was 28% sodium methoxide solution (methanol solution, 1.0 ml), and the mixture was stirred at room temperature for one hour. Added thereto was an aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was crystallized from hexane to give the desired 3-(4-ethylphenylmethyl)-1H-indazole (800 mg) as colorless crystals. APCI-Mass m/Z 237 (M+H).

Reference Example 111

5-Bromo-2-methyl-1-(5-(4-trifluoromethylphenyl)-2-thienylmethyl)benzene

(1) 4-Bromobenzotrifluoride and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-trifluoromethylphenyl)thiophene as colorless crystals.

(2) The above 2-(4-trifluoromethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the desired 5-bromo-2-methyl-1-(5-(4-trifluoromethylphenyl)-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 425/427 (M+H+MeOH).

Reference Example 112

5-Bromo-2-methyl-1-(5-(3-trifluoromethylphenyl)-2-thienylmethyl)benzene

(1) 3-Bromobenzotrifluoride and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-trifluoromethylphenyl)thiophene as colorless oil.

(2) The above 2-(3-trifluoromethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the desired 5-bromo-2-methyl-1-(5-(3-trifluoromethylphenyl)-2-thienylmethyl)benzene as colorless oil.

Reference Example 113 2-(4-Ethylphenyl)thiophene

2-Bromothiophene and 4-ethylphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give the target compound.

Reference Example 114 2-(4-Methylphenyl)thiophene

2-Bromothiophene and 4-methylphenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give the target compound.

Reference Example 115

2-(2,3-Dihydro-5-benzo[b]furanyl)thiophene

(1) 5,7-Dibromo-2,3-dihydrobenzo[b]furan (see WO 02/070020) (3.0 g) in diethyl ether was cooled to -78°C under argon atmosphere, and thereto was added dropwise n-butyl lithium (2.44 M hexane solution, 5.09 ml). The mixture was stirred at the same temperature for 30 minutes, and poured into a saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2,3-dihydrobenzo[b]furan (2.0 g) as pale yellow crystals, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2,3-dihydrobenzo[b]furan and thiophene-2-boronic acid were treated in a manner similar to

Reference Example 20-(1) to give the desired 2-(2,3-dihydro-5-benzo[b]furanyl)thiophene as pale yellow crystals. APCI-Mass m/Z 203 (M+H).

Reference Example 116

4-Bromo-2-(5-chloro-2-thienylmethyl)-1-fluoronaphthalene

(1) A solution of 2,2,6,6-tetramethylpiperidine (1.04 g) in tetrahydrofuran (15 ml) was cooled to -78°C under argon atmosphere, and thereto was added dropwise n-butyl lithium (1.58 M hexane solution, 4.43 ml). The reaction mixture was stirred at the same temperature for 30 minutes, and thereto was added dropwise a solution of 1-bromo-4-fluoronaphthalene (1.50 g) in tetrahydrofuran (12 ml) at -78°C. The mixture was stirred at the same temperature for one hour, and thereto was added dropwise a solution of 5-chloro-2-thiophenecarboxaldehyde (1.07 g) in tetrahydrofuran (11 ml) at -78°C. The mixture was stirred at the same temperature for 30 minutes, and thereto was added a saturated aqueous ammonium chloride solution, and the reaction mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by an aminosilane-treated silica gel column chromatography (hexane:ethyl acetate = 3:1) to give 4-bromo-1-fluoro-2-naphthyl-5-chloro-2-thienylmethanol (2.00 g) as pale yellow powder. APCI-Mass m/Z 353/355 ($M+H-H_2O$).

(2) The above 4-bromo-1-fluoro-2-naphthyl-5-chloro-2-thienylmethanol was treated in a manner similar to Reference Example 1-(2) to give the desired 4-bromo-2-(5-chloro-2-thienylmethyl)-1-fluoronaphthalene as a yellow solid.

Reference Example 117

5-Bromo-2,4-dimethyl-1-(5-phenyl-2-thienylmethyl)benzene

(1) 2,4-dimethylbenzoic acid (20.0 g) was suspended in chloroform (100 ml), and thereto were added oxalyl chloride (6.8 ml) and N,N-dimethylformamide (2 drops). The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in methanol (200 ml). The mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed successively with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give methyl 2,4-dimethylbenzoate as pale yellow oil, which was used in the subsequent step without further purification.

(2) To a mixture of the above methyl 2,4-dimethylbenzoate (19.75 g) and activated aluminum neutral oxide (120 g) was added dropwise bromine (9.25 ml) while stirring at room temperature. The mixture was stirred at room temperature for 8 hours, and diluted with diethyl ether (1000 ml). Insoluble materials were filtered off, and washed with diethyl ether (500 ml). The combined filtrate was washed successively with 10% aqueous sodium thiosulfate solution, a saturated aqueous sodium hydrogen carbonate solution and brine. The filtrate was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol (40 ml) to give methyl 5-bromo-2,4-dimethylbenzoate (6.34 g) as colorless crystals. APCI-Mass m/Z 243/245 (M+H).

(3) The above methyl 5-bromo-2,4-dimethylbenzoate was treated in a manner similar to Reference Example 4-(1) to give 5-bromo-2,4-dimethylbenzoic acid as colorless crystals. ESI-Mass m/Z 227/229 (M-H)

(4) The above 5-bromo-2,4-dimethylbenzoic acid and 2-phenylthiophene were treated in a manner similar to Reference Example 5 to give 5-bromo-2,4-dimethyl-1-(5-phenyl-2-thienylmethyl)benzene as colorless crystals. APCI-Mass m/Z 357/359 (M+H).

Reference Example 118

5-Bromo-1-(5-phenyl-2-thienylmethyl)-2-trifluoromethyl-benzene

(1) 5-Bromo-2-iodobenzoic acid (see Jorg Frahn, A.-Dieter Schluter *Synthesis* 1997, 1301-1304) was treated in a manner similar to Reference Example 117-(1) to give methyl 5-bromo-2-iodobenzoate as a brown solid.

(2) To a solution of the above methyl 5-bromo-2-iodobenzoate (4.65 g) in N-methyl-2-pyrrolydinone (20 ml) were added copper (I) bromide (235 mg) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (2.6 ml), and the mixture was stirred under heating at 120°C for 1.5 hours. The reaction mixture was cooled, and added thereto were 10% aqueous hydrochloric acid solution and ethyl acetate. Insoluble materials were filtered off, and an organic layer of the filtrate was washed with water for 4 times, and subsequently washed with a saturated aqueous sodium hydrogen carbonate solution and brine. The filtrate was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexan:ethyl acetate = 80:1) to give methyl 5-bromo-2-trifluoromethylbenzoate (3.55 g) as colorless oil.

(3) The above methyl 5-bromo-2-trifluoromethylbenzoate was treated in a manner similar to Reference Example 4-(1) to give 5-bromo-2-trifluoromethylbenzoic acid as pale brown crystals. ESI-Mass m/Z 267/269 (M-H).

(4) The above 5-bromo-2-trifluoromethylbenzoic acid and

2-phenylthiophene were treated in a manner similar to Reference Example 5-(1) to give 5-bromo-2-trifluoromethylphenyl 5-phenyl-2-thienyl ketone as pale yellow crystals. APCI-Mass m/Z 411/413 (M+H).

(5) To a mixed solution of the above 5-bromo-2-trifluoromethylphenyl 5-phenyl-2-thienyl ketone (670 mg) in methanol (20 ml) - tetrahydrofuran (10 ml) was added sodium borohydride (62 mg), and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in chloroform (10 ml) - acetonitrile (20 ml). Thereto was added triethylsilane (0.78 ml), and the mixture was cooled to 0°C. Thereto was added dropwise boron trifluoride · diethyl ether complex (0.52 ml). The mixture was stirred at room temperature for 45 minutes, and added thereto was a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane) to give the desired 5-bromo-1-(5-phenyl-2-thienylmethyl)-2-trifluoromethylbenzene (565 mg) as colorless oil.

Reference Example 119

5-Bromo-1-(5-(3-ethylphenyl)-2-thienylmethyl)-2-methylbenzene

(1) 1-Bromo-3-ethylbenzene and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(3-ethylphenyl)thiophene as a pale yellow liquid.

(2) The above 2-(3-ethylphenyl)thiophene and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 9 to give 5-bromo-1-(5-(3-ethylphenyl)-2-thienylmethyl)-2-methylbenze

ne as pale yellow oil. APCI-Mass m/Z 371/373 (M+H).

Reference Example 120

5-Bromo-2-methyl-1-(5-(2-pyridyl)-2-thienylmethyl)benzene

(1) 2-(2-Pyridyl)thiophene and 5-bromo-2-mehtylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7-(1) to give 5-bromo-2-methylphenyl-5-(2-pyridyl)-2-thienylmethanol as colorless oil. APCI-Mass m/Z 360/362 (M+H).

(2) A solution of the above 5-bromo-2-methylphenyl-5-(2-pyridyl)-2-thienylmethanol (1.59 g) in trifluoroacetic acid (40 ml) was cooled to 0°C, and thereto were added gradually sodium triacetoxyborohydride (4.68 g). The mixture was stirred at room temperature for one hour, and cooled again to 0°C. 10% aqueous sodium hydroxide solution was added thereto to basify the reaction mixture. The mixture was extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to give the desired 5-bromo-2-methyl-1-(5-(2-pyridyl)-2-thienylmethyl)benzene (1.38 g) as a colorless solid. APCI-Mass m/Z 344/346 (M+H).

Reference Example 121

2-(5-Fluoro-2-thienyl)thiophene

2,2′-Bithiophene (7.40 g) in tetrahydrofuran(90 ml) was cooled to -78°C under argon atmosphere, and thereto were added dropwise n-butyl lithium (1.59 M hexane solution, 28.0 ml). The mixture was stirred at 0°C for one 30 minutes, and cooled again to -78°C. Added thereto was N-fluorobenzenesulfonimide (15.5 g), and the mixture was gradually warmed, and stirred at room temperature for 17 hours. The reaction mixture was poured into ice-cold

water, and the solution was extracted with hexane twice, and the extract was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane) to give 2-(5-fluoro-2-thienyl)thiophene (5.89 g) as colorless oil.

Reference Example 122

5-Bromo-2-methyl-1-(5-(3-pyridyl)-2-thienylmethyl)benzene

2-(3-Pyridyl)thiophene was treated in a manner similar to Reference Example 120 to give the target compound as colorless crystals. APCI-Mass m/Z 344/346 (M+H).

Reference Example 123

5-Bromo-1-(5-(4-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene

(1) *p*-Bromoanisole and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(4-methoxyphenyl)thiophene as a pale yellow solid. APCI-Mass m/Z 191 (M+H).

(2) The above 2-(4-methoxyphenyl)thiophene and 4-bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) were treated in a manner similar to Reference Example 5 to give 5-bromo-1-(5-(4-methoxyphenyl)-2-thienylmethyl)-2-methylbenzene as a pale yellow solid. APCI-Mass m/Z 373/375 (M+H).

Reference Example 124

5-bromo-2-methyl-1-(5-(1,2-Methylenedioxybenzen-4-yl)-2-thienylmethyl)benzene

4-Bromo-1,2-(methylenedioxy)benzene was treated in a manner similar to Reference Example 119 to give the target compound as colorless powder.

Reference Example 125

5-Bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl)benzene

(1) To a solution of 5-bromo-2-chlorobenzyl alcohol (10.66 g) in toluene (100 ml) solution were added thionyl chloride (10 ml), and pyridine (2 drops), and the mixture was stirred under heating at 100°C overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed successively with water, a 10% aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzyl chloride as pale yellow crystals, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2-chlorobenzyl chloride was dissolved in acetonitrile (100 ml), and the mixture was cooled to 0°C. Added thereto was tetraethylammonium cyanide (8.8 g), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed successively with water, 10% aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorophenylacetonitrile as a pale yellow solid, which was used in the subsequent step without further purification.

(3) The above 5-bromo-2-chlorophenylacetonitrile was added to water (90 ml) - sulfuric acid (75 ml), and the mixture was stirred under heating at 160°C overnight. The mixture was further diluted with water, and cooled to 0°C. The solvent was removed by decant, and the residue was dissolved in diethyl ether. The solution was washed with water and brine, and extracted with

10% sodium hydroxide. To the extract was added concentrated hydrochloric acid to make the solution acidic. The precipitates were collected by filtration, and purified by silica gel column chromatography (chloroform) to give 5-bromo-2-chlorophenylacetic acid (6.67 g) as colorless crystals. ESI-Mass m/Z 247/249 (M-H).

(4) The above 5-bromo-2-chlorophenylacetic acid was treated in a manner similar to Reference Example 118-(4) and (5) to give the desired 5-bromo-2-chloro-1-(2-(5-phenyl-2-thienyl)ethyl)benzene as a pale yellow solid. APCI-Mass m/Z 377/379 (M+H).

Reference Example 126

5-Bromo-1-(5-(6-fluoro-2-pyridyl)-2-thienylmethyl)2-methylbenzene

(1) 2-Bromo-6-fluoropyridine and thiophene-2-boronic acid were treated in a manner similar to Reference Example 20-(1) to give 2-(6-fluoro-2-pyridyl)thiophene as yellow oil. APCI-Mass m/Z 180 (M+H).

(2) The above 2-(6-fluoro-2-pyridyl)thiophene was treated in a manner similar to Reference Example 120 to give the desired 5-bromo-1-(5-(6-fluoro-2-pyridyl)-2-thienylmethyl)2-methylbenzene as a colorless solid. APCI-Mass m/Z 362/364 (M+H).

Reference Example 127

5-Bromo-2-methyl-1-(5-trifluoromethyl-2-thienylmethyl)-benzene

2-Trifluoromethylthiophene (see Japanese Unexamined Patent Publication No. 2000-34239) and 5-bromo-2-methylbenzaldehyde obtained in Reference Example 4 were treated in a manner similar to Reference Example 7 to give the target compound as colorless oil.

Reference Example 128

5-Bromo-1-(5-(5-fluoro-2-thienyl)-2-thienylmethyl)-2-methylbenzene

5-Bromo-2-methylbenzoic acid obtained in Reference Example 4-(1) and 2-(5-fluoro-2-thienyl)thiophene obtained in Reference Example 121 were treated in a manner similar to Reference Example 5 to give the target compound as a colorless solid. APCI-Mass m/Z 367/369 (M+H).

Reference Example 129

3-Bromo-2-fluoro-6-methyl-1-(5-phenyl-2-thienylmethyl)benzene

4-Bromo-3-fluorotoluene and 5-phenyl-2-thiophenecarboxaldehyde were treated in a manner similar to Reference Example 116 to give the target compound as pale blue powders. APCI-Mass m/Z 361/363 (M+H).

Reference Example 130

5-Bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl)benzene

(1) 5-Bromo-2-chlorophenylacetic acid (2.0 g) obtained in Reference Example 125-(3) was dissolved in dichloromethane (40 ml), and thereto were added oxalyl chloride (0.77 ml) and N,N-dimethylformamide (one drop) at 0°C. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorophenylacetyl chloride, which was used in the subsequent step without further purification.

(2) A solution of potassium t-butoxide (1.35 g) in tetrahydrofuran (20 ml) was cooled to 0°C, and thereto was added methyl isocyanoacetate (1.33 ml). Then, a solution of the above 5-bromo-2-chlorophenylacetyl chloride in tetrahydrofuran (20 ml) was added thereto, and the mixture was stirred at 0°C for 2 hours, and then at room temperature overnight. The mixture

was cooled again to 0°C. 10% aqueous citric acid solution was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to give 5-bromo-2-chloro-1-(4-methoxycarbonyl-5-oxazolylmethyl)benzene (1.12 g) as a yellow solid. APCI-Mass m/Z 330/332 (M+H).

(3) The above 5-bromo-2-chloro-1-(4-methoxycarbonyl-5-oxazolylmethyl)benzene (1.37 g) was heated under reflux in 6N aqueous hydrochloric acid solution (20 ml) overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in methanol, and treated with carbon powder. The carbon powder was filtered off, and the filtrate was evaporated under reduced pressure to give crude 1-(3-amino-2-oxopropyl)-5-bromo-2-chlorobenzene·hydrochloride (1.73 g) as a pale brown solid, which was used in the subsequent step without further purification. APCI-Mass m/Z 262/264 (M+H).

(4) A mixed solution of the above 1-(3-amino-2-oxopropyl)-5-bromo-2-chlorobenzene·hydrochloride (1.70 g) in ethyl acetate (30 ml) - water (15 ml) was cooled to 0°C. Added thereto were benzoyl chloride (0.99 ml) and sodium hydrogen carbonate (2.39 g), and the mixture was stirred at the same temperature for 3 hours. The organic layer was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (chloroform:ethyl acetate = 95:5) to give 1-(3-benzoylamino-2-oxopropyl)-5-bromo-2-chlorobenzene (710 mg) as a colorless solid. APCI-Mass m/Z 366/368 (M+H).

(5) To a solution of the above

1-(3-benzoylamino-2-oxopropyl)-5-bromo-2-chlorobenzene (710 mg) in toluene (20 ml) was added Lawesson reagent (2.35 g), and the mixture was heated under reflux for 2 hours. The reaction mixture was cooled, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 90:10) to give the desired 5-bromo-2-chloro-1-(2-phenyl-5-thiazolylmethyl)benzene (512 mg) as a colorless solid. APCI-Mass m/Z 364/366 (M+H).

Reference Example 131

t-Butyl 5-bromo-2-chlorobenzoic acid

To a solution of 5-bromo-2-chlorobenzoic acid (11.75 g) in N,N-dimethylformamide (50 ml) was added 1,1'-carbonyldiimidazole (8.10 g), and the mixture was stirred under heating at 40°C for one hour. Thereto were added t-butanol (7.40 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (7.60 g), and the mixture was further stirred under heating at 40°C overnight. The mixture was diluted with diethyl ether, and washed successively with water (3 times), 2% aqueous hydrochloric acid solution (twice), a saturated aqueous sodium hydrogen carbonate solution and brine. The mixture was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give t-butyl 5-bromo-2-chlorobenzoate (12.53 g) as pale yellow oil.

Reference Example 132

5-Bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene

(1) A solution of 5-bromo-2-chloro-1-(6-methoxybenzo[b]thiophen-2-ylmethyl)benzene (2.70 g) obtained in Reference Example 46 in dichloromethane (27 ml) was cooled to 0°C under argon atmosphere, and thereto was added

dropwise boron tribromide (0.83 ml). The mixture was warmed to room temperature, and stirred for 30 minutes. The mixture was basified with a saturated aqueous sodium hydrogen carbonate solution, and subsequently, the reaction mixture was made acidic with a saturated aqueous citric acid solution. The mixture was extracted with chloroform, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was crystallized from chloroform-hexane to give 5-bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene (2.01 g) as pale green crystals. ESI-Mass m/Z 351/353 (M-H).

(2) The above 5-bromo-2-chloro-1-(6-hydroxy-benzo[b]thiophen-2-ylmethyl)benzene (500 mg) was dissolved in N,N-dimethylformamide (5 ml), and thereto were added iodoethane (0.23 ml) and potassium carbonate (390 mg). The mixture was stirred at room temperature for 2 days. Added thereto was water, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 98:2 -80:20) to give the desired 5-bromo-2-chloro-1-(6-ethoxybenzo[b]thiophen-2-ylmethyl)benzene (492 mg) as pale pink oil. APCI-Mass m/Z 381/383 (M+H).

<u>Reference Example 133</u>

<u>5-Bromo-2-chloro-3-(5-phenyl-2-thienylmethyl)thiophene</u>

5-Bromo-2-chloro-3-thiophenecarboxylic acid (see Japanese Unexamined Patent Publication No. 10-324632) and 2-phenylthiophene were treated in a manner similar to Reference Example 5 to give the target compound as a colorless solid. APCI-Mass m/Z 367/369 (M+H).

Reference Example 134

6-Fluoro-2-pyridylboronic acid pinacol ester

A solution of 2-bromo-6-fluoropyridine (1.0 g) in tetrahydrofuran (10 ml) was cooled to -78°C under argon atmosphere, and thereto was added a solution of n-butyl lithium (2.59 M hexane solution, 2.24 ml) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 45 minutes, and thereto was added dropwise a solution of triisopropoxyborane (1.28 g) in tetrahydrofuran (10 ml). The mixture was stirred at the same temperature for 2 hours, warmed, and further stirred at room temperature for one hour. Subsequently, a solution of pinacol (0.91 g) in tetrahydrofuran (10 ml) was added dropwise thereto, and stirred at room temperature for 20 minutes. Insoluble materials were filtered off. The filtrate was extracted with 2.5% sodium hydroxide, and the extract was cooled to 0°C, and was made weakly acidic with 2N aqueous hydrochloric acid solution. It was extracted with diethyl ether, washed with a small amount of brine, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was solidified with hexane to give 6-fluoro-2-pyridylboronic acid pinacol ester (850 mg) as a colorless solid. APCI-Mass m/Z 224 (M+H).

Reference Example 135

5-Bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl)benzene

(1) 5-Bromo-2-chlorobenzoic acid was treated in a manner similar to Reference Example 4-(2) to give N-methoxy-N-methyl-5-bromo-2-chlorobenzamide as a colorless solid. APCI-Mass m/Z 278/280 (M+H).

(2) The above N-methoxy-N-methyl-5-bromo-2-chlorobenzamide and 2,5-dibromopyridine were treated in a manner similar to Reference Example 31-(4) to give 5-bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone as a pale yellow solid. APCI-Mass m/Z

374/376 (M+H).

(3) The above 5-bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone and phenylboronic acid were treated in a manner similar to Reference Example 20-(1) to give 5-bromo-2-chlorophenyl 6-phenyl-3-pyridyl ketone as yellow crystals. APCI-Mass m/Z 372/374 (M+H).

(4) The above 5-bromo-2-chlorophenyl 6-phenyl-3-pyridyl ketone was treated in a manner similar to Reference Example 14-(1) to give the desired 5-bromo-2-chloro-1-(6-phenyl-3-pyridylmethyl)benzene as colorless crystals. APCI-Mass m/Z 358/360 (M+H).

Reference Example 136

5-Bromo-2-chloro-1-(6-isopropyloxybenzo[b]thiophen-2-ylmethyl)benzene

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene obtained in Reference Example 132-(1) and 2-iodopropane were treated in a manner similar to Reference Example 132-(2) to give the titled compound. APCI-Mass m/Z 395/397 (M+H).

Reference Example 137 4-Bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl)naphthalene

(1) A solution of 2,2,6,6-tetramethylpiperidine (4.13 ml) in tetrahydrofuran (40 ml) was cooled to -78°C under argon atmosphere, and added dropwise thereto was n-butyl lithium (2.44 M hexane solution, 10.0 ml). The mixture was stirred at the same temperature for 30 minutes, and added dropwise thereto at -78°C was a solution of 1-bromo-4-fluoronaphthalene (5.0 g) in tetrahydrofuran (20 ml). The mixture was stirred at the same temperature for 1 hour, and added dropwise thereto at -78°C was N,N-dimethylformamide (5.16 ml). The mixture was stirred at the same temperature for 1 hour, and added thereto was a

saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was crystallized from diisopropyl ether and hexane to give 4-bromo-1-fluoro-2-naphthaldehyde (4.43 g) as pale yellow crystals. APCI-Mass m/Z 267/269 ($M+NH_4$).

(2) The above 4-bromo-1-fluoro-2-naphthaldehyde and 2-(2-pyridyl)thiophene were treated in a manner similar to Reference Example 120 to give the desired 4-bromo-1-fluoro-2-(5-(2-pyridyl)-2-thienylmethyl)naphthalene as colorless powder. APCI-Mass m/Z 398/400 (M+H).

<u>Reference Example 138</u>

<u>5-Bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene</u>

(1) 5-Bromo-2-chlorophenyl 6-bromo-3-pyridyl ketone (3.2 g) from Reference Example 135-(2) was dissolved in tetrahydrofuran (80 ml), and added thereto were triethylaluminium (1.0 M hexane solution, 9.9 ml), tetrakis(triphenylphosphine)palladium(0) (570 mg) and cerium(III) chloride (7.3 g), and the mixture was stirred at 30°C for 1.5 hours. The reaction mixture was diluted with methanol, and the reaction solution was basified with a saturated aqueous sodium hydrogen carbonate solution. The insoluble materials were filtered off and, the filtrate was extracted with ethyl acetate and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 99:1 - 85:15) to give 5-bromo-2-chlorophenyl 6-ethyl-3-pyridyl ketone (1.98 g) as a colorless solid. APCI-Mass m/Z 324/326 (M+H).

(2) The above 5-bromo-2-chlorophenyl 6-ethyl-3-pyridyl ketone was treated in a manner similar to Reference Example 14-(1) to give the desired

5-bromo-2-chloro-1-(6-ethyl-3-pyridylmethyl)benzene as a colorless oil. APCI-Mass m/Z 310/312 (M+H).

Reference Example 139 6-Ethylbenzo[b]thiophene

(1) 4-Bromo-2-flurobenzaldehyde and ethyl thioglycolate were treated in a manner similar to Reference Example 31-(1) to give 6-bromo-2-ethoxycarbonylbenzo[b]thiophene as a colorless solid.

(2) The above 6-bromo-2-ethoxycarbonylbenzo[b]thiophene was treated in a manner similar to Reference Example 138-(1) to give 6-ethyl-2-ethoxycarbonylbenzo[b]thiophene as colorless oil. APCI-Mass m/Z 235 (M+H).

(3) The above 6-ethyl-2-ethoxycarbonylbenzo[b]thiophene (1.26 g) was dissolved in tetrahydrofuran (4 ml) and methanol (8 ml), and added thereto was lithium hydroxide monohydrate (677 mg), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in water and the solution was made acidic with a 10% aqueous hydrochloric acid solution. The precipitates were collected by filtration and washed with water to give 6-ethylbenzo[b]thiophen-2-ylcarboxylic acid (1.15 g) as colorless crystals. ESI-I-Mass m/Z 205 (M-H).

(4) The above 6-ethylbenzo[b]thiophen-2-ylcarboxylic acid was tread in a manner similar to Reference Example 47-(2) to give the desired 6-ethylbenzo[b]thiophene as colorless oil.

Reference Example 140

5-Bromo-2-chloro-1-(1-oxo-2-isoindolinylmethyl)benzene

(1) 5-Bromo-2-chlorobenzyl alcohol (3.0 g) was dissolved in toluene (30 ml), and added thereto were thionyl chloride (2.35 ml) and pyridine (two drops), and the mixture was heated under stirring at 100°C for 2 hours. The mixture was cooled, washed with a saturated aqueous sodium hydrogen carbonate solution and

brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5-bromo-2-chlorobenzyl chloride (3.34 g) as pale brown oil, which was used in the subsequent step without further purification.

(2) The above 5-bromo-2-chlorobenzyl chloride (3.34 g) was dissolved in N,N-dimethylformamide (30 ml), and added thereto was potassium phthalimide (2.63 g), and the mixture was heated under stirring at 70°C for 3 hours. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was crystallized from diisopropyl ether to give 5-bromo-2-chloro-1-(phthalimid-2-ylmethyl)-benzene (3.33 g) as colorless crystals. APCI-Mass m/Z 350/352 (M+H).

(3) The above 5-bromo-2-chloro-1-(phthalimid-2-ylmethyl)-benzene (4.3 g) was dissolved in acetic acid (43 ml), and added thereto was zinc powder (8.02 g), and the mixture was heated at reflux for 3 days. The mixture was cooled and diluted with chloroform and it was basified with an aqueous sodium hydroxide solution. The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 6:1 - 4:1) to give the desired 5-bromo-2-chloro-1-(1-oxo-2-isoindolinylmethyl)benzene (1.39 g) as colorless powder. APCI-Mass m/Z 336/338 (M+H).

Reference Example 141

5-Bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl)benzene

(1) A solution of 1-phenyl-4-bromopyrazole (see M. A. Khan, et al., Can. J. Chem., (1963) 41 1540) (2.23 g) in diethyl ether (30 ml) wad cooled to -78°C under argon atmosphere, and added

dropwise thereto was n-butyl lithium (1.59 M hexane solution, 6.9 ml). The mixture was stirred at -20°C to -10°C for 5 hours, and added dropwise thereto at the same temperature was a solution of 5-bromo-2-chlorobenzaldehyde (2.19 g) obtained in Reference Example 16-(1) in diethyl ether (30 ml). The mixture was stirred at the same temperature for 30 minutes, and added thereto was tetrahydrofuran (30 ml), and the mixture was stirred at 0°C for further 30 minutes. A saturated aqueous ammonium chloride solution was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 83:17 - 80:20) to give 5-bromo-2-chlorophenyl-1-phenyl-4-pyrazolylmethanol (831 mg) as yellow oil. APCI-Mass m/Z 363/365 (M+H).

(2) The above 5-bromo-2-chlorophenyl-1-phenyl-4-pyrazolylmethanol was treated in a manner similar to Reference Example 120-(2) to give the desired 5-bromo-2-chloro-1-(1-phenyl-4-pyrazolylmethyl)benzene as colorless powder. APCI-Mass m/Z 347/349 (M+H).

<u>Reference Example 142</u>

<u>5-Bromo-2-chloro-1-(6-n-propyloxybenzo[b]thiophen-2-ylmethyl)benzene</u>

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene obtained in Reference Example 132-(1) and 1-bromopropane were treated in a manner similar to Reference Example 132-(2) to give the target compound. APCI-Mass m/Z 395/397 (M+H).

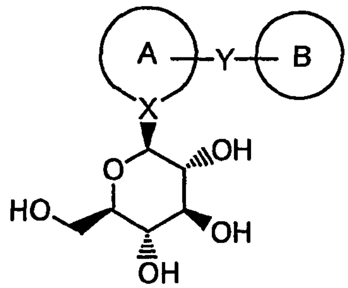
<u>Reference Example 143</u>

<u>5-Bromo-2-chloro-1-(6-(2-fluoroethyloxy)benzo[b]thiophen-2-ylmethyl)benzene</u>

5-Bromo-2-chloro-1-(6-hydroxybenzo[b]thiophen-2-ylmethyl)benzene obtained in Reference Example 132-(1) and 1-bromo-2-fluoroethane were treated in a manner similar to Reference Example 132-(2) to give the target compound.
APCI-Mass m/Z 399/401 (M+H).

CLAIMS

1. A compound of formula:



(I)

wherein Ring A and Ring B are one of the followings: (1) Ring A is an optionally substituted unsaturated monocyclic heterocyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring, (2) Ring A is an optionally substituted benzene ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, or an optionally substituted unsaturated fused heterobicyclic ring wherein Y is linked to the heterocyclic ring of said fused heterobicyclic ring, or (3) Ring A is an optionally substituted unsaturated fused heterobicyclic ring, wherein the sugar moiety X-(sugar) and the moiety -Y-(Ring B) are both on the same heterocyclic ring of said fused heterobicyclic ring, and Ring B is an optionally substituted unsaturated monocyclic heterocyclic ring, an optionally substituted unsaturated fused heterobicyclic ring, or an optionally substituted benzene ring;
X is a carbon atom or a nitrogen atom; and
Y is $-(CH_2)_n-$ (wherein n is 1 or 2);
a pharmaceutically acceptable salt thereof, or a prodrug thereof.

2. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1, wherein the optionally substituted unsaturated monocyclic heterocyclic

ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxyl group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl

group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidene- methyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenyl- carbonyl group, a cycloalkynyl- carbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxy- carbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxy- carbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cyclo- alkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cyclo- alkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclyl- carbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio

group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoyl- amino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkyl- sulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cyclo- alkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cyclo- alkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, and a heterocyclylsulfonyl group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-5 substituents selected from the group consisting of a halogen atom, a nitro group, a cyano group, a hydroxy group, a mercapto group, a carboxyl group, a sulfo group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkynyl group, an aryl group, a heterocyclyl group, an alkoxy group, an alkenyloxy group, an alkynyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, a cycloalkynyloxy group, an aryloxy group, a heterocyclyloxy group, an alkanoyl group, an alkenylcarbonyl group, an alkynylcarbonyl group, a cycloalkylcarbonyl group, a cycloalkenylcarbonyl group, a cycloalkynylcarbonyl group, an arylcarbonyl group, a heterocyclylcarbonyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a cycloalkyloxycarbonyl group, a cycloalkenyloxycarbonyl group, a cycloalkynyloxycarbonyl group, an aryloxycarbonyl group, a heterocyclyloxycarbonyl

group, an alkanoyloxy group, an alkenylcarbonyloxy group, an alkynylcarbonyloxy group, a cycloalkylcarbonyloxy group, a cycloalkenylcarbonyloxy group, a cycloalkynylcarbonyloxy group, an arylcarbonyloxy group, a heterocyclylcarbonyloxy group, an alkylthio group, an alkenylthio group, an alkynylthio group, a cycloalkylthio group, a cycloalkenylthio group, a cycloalkynylthio group, an arylthio group, a heterocyclylthio group, an amino group, a mono- or di-alkylamino group, a mono- or di-alkanoylamino group, a mono- or di-alkoxycarbonylamino group, a mono- or di-arylcarbonylamino group, an alkylsulfinylamino group, an alkylsulfonylamino group, an arylsulfinylamino group, an arylsulfonylamino group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a mono- or di-arylcarbamoyl group, an alkylsulfinyl group, an alkenylsulfinyl group, an alkynylsulfinyl group, a cycloalkylsulfinyl group, a cycloalkenylsulfinyl group, a cycloalkynylsulfinyl group, an arylsulfinyl group, a heterocyclylsulfinyl group, an alkylsulfonyl group, an alkenylsulfonyl group, an alkynylsulfonyl group, a cycloalkylsulfonyl group, a cycloalkenylsulfonyl group, a cycloalkynylsulfonyl group, an arylsulfonyl group, a heterocyclylsulfonyl group, an alkylene group, an alkyleneoxy group, an alkylenedioxy group, and an alkenylene group.

3. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1, wherein the optionally substituted unsaturated monocyclic heterocyclic ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a

cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a

cycloalkenyl group, a cycloalkyloxy group, an aryl group, an aryloxy group, an arylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, an arylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfonyl group, a heterocyclyl group, an alkylene group, an alkyleneoxy group, an alkylenedioxy group, and an alkenylene group.

4. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1, wherein the optionally substituted unsaturated monocyclic heterocyclic ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a

cycloalkylidenemethyl group, an alkoxy group, an alkylthio group, an alkylsulfonyl group, an alkylsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkyl- sulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, phenylsulfonyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

wherein the substituents on the unsaturated monocyclic heterocyclic ring, the unsaturated fused heterobicyclic ring and the benzene ring may further be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, a mono- or di-alkylamino group, a carboxyl group, an alkoxycarbonyl group, a phenyl group, an alkylenedioxy group,

an alkyleneoxy group, and an oxo group.

5. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1, wherein the optionally substituted unsaturated monocyclic heterocyclic ring is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, and an oxo group;

the optionally substituted unsaturated fused heterobicyclic ring is an unsaturated fused heterobicyclic ring which may optionally be substituted by 1-3 substituents independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxy group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, and an oxo group; and

the optionally substituted benzene ring is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, an alkoxy group, an alkanoyl group, a mono- or di-alkylamino group, an alkanoylamino group, an alkoxycarbonylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, a phenyl group, a heterocyclyl group, an alkylene group, and an alkenylene group;

wherein the substituents on the unsaturated monocyclic heterocyclic ring, the unsaturated fused heterobicyclic ring

and the benzene ring may further be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, a mono- or di-alkylamino group, a carboxyl group, a hydroxy group, a phenyl group, an alkylenedioxy group, an alkyleneoxy group, and an alkoxycarbonyl group.

6. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1, wherein Ring A and Ring B are:

(1) Ring A is an unsaturated monocyclic heterocyclic ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkl-sulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, and an oxo group, and

Ring B is an unsaturated monocyclic heterocyclic ring, an unsaturated fused heterobicyclic ring, or a benzene ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alkl-sulfinyl group, an amino group, a mono- or di-alkylamino group,

a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group; or

(2) Ring A is a benzene ring which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a phenylsulfonyl group, a heterocyclyl group, an alkylene group, and an alkenylene group, and

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a nitro group, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, an alkoxy group, an alkanoyl group, an alkylthio group, an alkylsulfonyl group, an alklsulfinyl group, an amino group, a mono- or di-alkylamino group, a sulfamoyl group, a mono- or di-alkylsulfamoyl group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkylsufonylamino group, a phenyl group, a phenoxy group, a phenylsulfonylamino group, a

phenylsulfonyl group, a heterocyclyl group, an alkylene group and an oxo group;

wherein the substituent on Ring A and Ring B may optionally be substituted by 1-3 substituents, independently selected from the group consisting of a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkanoyl group, a mono- or di-alkylamino group, a carboxyl group, a hydroxy group, a phenyl group, an alkylenedioxy group, an alkyleneoxy group, and an alkoxycarbonyl group.

7. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1, wherein Y is $-CH_2-$ and is linked at the 3-position of Ring A, with respect to X being the 1-position,

Ring A is a benzene ring which is substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, and a phenyl group, and a lower alkenylene group, and

Ring B is an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a phenyl-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxy phenyl group, a lower alkylenedioxyphenyl group, a lower alkyleneoxy phenyl group, a mono- or di-lower alkylaminophenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, a lower alkoxyheterocyclyl group, and a mono- or di-lower alkylaminoheterocycyclyl group.

8. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1, wherein Y

is $-CH_2-$ and is linked at the 3-position of Ring A, with respect to X being the 1-position,

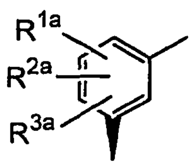
Ring A is an unsaturated monocyclic heterocyclic ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halogen atom, a lower alkoxy group, and an oxo group, and

Ring B is (a) a benzene ring which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxyphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, and a lower alkoxyheterocyclyl group, or (b) an unsaturated monocyclic heterocyclic ring or an unsaturated fused heterobicyclic ring, each of which may be substituted by 1-3 substituents selected from the group consisting of a lower alkyl group, a halo-lower alkyl group, a halogen atom, a lower alkoxy group, a halo-lower alkoxy group, a phenyl group, a halophenyl group, a cyanophenyl group, a lower alkylphenyl group, a halo-lower alkylphenyl group, a lower alkoxyphenyl group, a halo-lower alkoxyphenyl group, a heterocyclyl group, a haloheterocyclyl group, a cyanoheterocyclyl group, a lower alkylheterocyclyl group, a lower alkoxyheterocyclyl group, and a lower alkoxyheterocyclyl group.

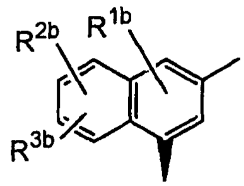
9. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to any one of claims 1-8, wherein the unsaturated monocyclic heterocyclic ring is furan, thiophene, oxazole, isoxazole, triazole, tetrazole, pyrazole, pyridine, pyrimidine, pyrazine, dihydroisoxazole, dihydropyridine, or thiazole; and

the unsaturated fused heterobicyclic ring is indoline, isoindoline, benzothiazole, benzoxazole, indole, indazole, quinoline, isoquinoline, benzothiophene, benzofuran, thienothiophene, or dihydroisoquinoline.

10. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1, wherein Ring A is

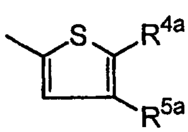


or



wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a hydroxy group, an alkoxy group, an alkyl group, a haloalkyl group, a haloalkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an alkoxyalkoxy group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkylidenemethyl group, a cycloalkenyl group, a cycloalkyloxy group, a phenyl group, a phenylalkoxy group, a cyano group, a nitro group, an amino group, a mono- or di-alkylamino group, an alkanoylamino group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group, an alkanoyl group, an alkylsulfonylamino group, a phenylsulfonylamino group, an alkylsulfinyl group, an alkylsulfonyl group, or a phenylsulfonyl group, and

Ring B is



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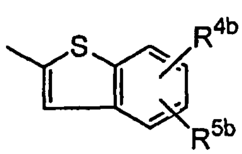
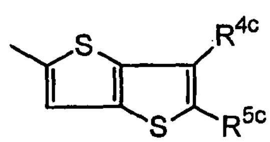


or



wherein R^{4a} and R^{5a} are each independently a hydrogen atom; a halogen atom; a hydroxy group; an alkoxy group; an alkyl group; a haloalkyl group; a haloalkoxy group; a hydroxyalkyl group;

an alkoxyalkyl group; a phenylalkyl group; an alkoxyalkoxy group; a hydroxyalkoxy group; an alkenyl group; an alkynyl group; a cycloalkyl group; a cycloalkylidenemethyl group; a cycloalkenyl group; a cycloalkyloxy group; a phenyloxy group; a phenylalkoxy group; a cyano group; a nitro group; an amino group; a mono- or di-alkylamino group; an alkanoylamino group; a carboxyl group; an alkoxycarbonyl group; a carbamoyl group; a mono- or di-alkylcarbamoyl group; an alkanoyl group; an alkylsulfonylamino group; a phenylsulfonylamino group; an alkylsulfinyl group; an alkylsulfonyl group; a phenylsulfonyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group, a haloalkoxy group, an alkylenedioxy group, an alkyleneoxy group, or a mono- or di-alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group or a haloalkoxy group, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form an alkylene group; and

R^{4b}, R^{5b}, R^{4c} and R^{5c} are each independently a hydrogen atom; a halogen atom; a hydroxy group; an alkoxy group; an alkyl group; a haloalkyl group; a haloalkoxy group; a hydroxyalkyl group; an alkoxyalkyl group; a phenylalkyl group; an alkoxyalkoxy group; a hydroxyalkoxy group; an alkenyl group; an alkynyl group; a cycloalkyl group; a cycloalkylidenemethyl group; a cycloalkenyl group; a cycloalkyloxy group; a phenyloxy group; a phenylalkoxy group; a cyano group; a nitro group; an amino group; a mono- or di-alkylamino group; an alkanoylamino group; a carboxyl group; an alkoxycarbonyl group; a carbamoyl group; a mono- or di-alkylcarbamoyl group; an alkanoyl group; an alkylsulfonylamino group; a phenylsulfonylamino group; an alkylsulfinyl group; an alkylsulfonyl group; a phenylsulfonyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group,

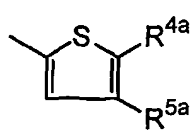
a haloalkoxy group, a methylenedioxy group, an ethyleneoxy group, or a mono- or di-alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a haloalkyl group, an alkoxy group or a haloalkoxy group.

11. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 10, wherein R^{1a}, R^{2a}, R^{3a}, R^{1b}, R^{2b}, and R^{3b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a phenyl group;

R^{4a} and R^{5a} are each independently a hydrogen atom; a halogen atom; a lower alkyl group; a halo-lower alkyl group; a phenyl-lower alkyl group; a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a methylenedioxy group, an ethyleneoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form a lower alkylene group; and

R^{4b}, R^{5b}, R^{4c} and R^{5c} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group.

12. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 11, wherein Ring B is

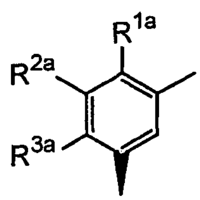


,

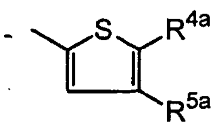
wherein R^{4a} is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, a

methylenedioxy group, an ethyleneoxy group, or a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group, and R^{5a} is a hydrogen atom, or R^{4a} and R^{5a} are bonded to each other at the terminals thereof to form a lower alkylene group.

13. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 12, wherein Ring A is



wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms; and Ring B is



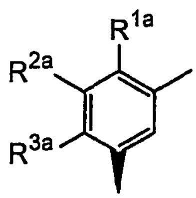
wherein R^{4a} is a phenyl group optionally substituted by a substituent selected from the group consisting of a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a halo-lower alkoxy group, and a mono- or di-lower alkylamino group; or a heterocyclyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, or a lower alkoxy group, and R^{5a} is a hydrogen atom, and Y is $-CH_2-$.

14. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 13, wherein R^{4a} is a phenyl group optionally substituted by a halogen atom, a cyano group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group; or a heterocyclyl group optionally substituted by a halogen atom,

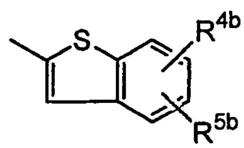
a cyano group, a lower alkyl group, or a lower alkoxy group.

15. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 14, wherein, the heterocyclyl group is a thienyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, pyrazolyl group, a thiazolyl group, a quinolyl group, or a tetrazolyl group.

16. The compound, the pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 10, wherein Ring A is



wherein R^{1a} is a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^{2a} and R^{3a} are hydrogen atoms; and Ring B is



wherein R^{4b} and R^{5b} are each independently a hydrogen atom, a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a halo-lower alkoxy group.

17. The compound, a pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1, wherein the compound is selected from the group consisting of:

1-(β-D-glucopyranosyl)-4-chloro-3-(6-ethylbenzo[b]thiophen-2-ylmethyl)benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(5-thiazolyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-(5-phenyl-2-thienyl-methyl)benzene;

1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene;

1-(β-D-glucopyranosyl)-4-chloro-3-[5-(2-pyrimidinyl)-2-

thienylmethyl]benzene;
1-(β-D-glucopyranosyl)-4-methyl-3-[5-(2-pyrimidinyl)-2-thienylmethyl]benzene;
1-(β-D-glucopyranosyl)-4-chloro-3-[5-(3-cyanophenyl)-2-thienylmethyl]benzene;
1-(β-D-glucopyranosyl)-4-chloro-3-[5-(4-cyanophenyl)-2-thienylmethyl]benzene;
1-(β-D-glucopyranosyl)-4-methyl-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;
1-(β-D-glucopyranosyl)-4-chloro-3-[5-(6-fluoro-2-pyridyl)-2-thienylmethyl]benzene;
1-(β-D-glucopyranosyl)-4-methyl-3-[5-(3-difluoromethyl-phenyl)-2-thienylmethyl]benzene;
the pharmaceutically acceptable salt thereof; and
the prodrug thereof.

18. A pharmaceutical composition, which comprises the compound as set forth in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and a pharmaceutically acceptable carrier or diluent.

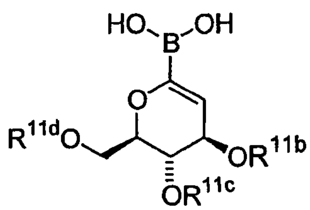
19. The pharmaceutical composition according to claim 18, which further comprises another antidiabetic agent.

20. A method for treating or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of the compound, a pharmaceutically acceptable salt thereof, or a prodrug thereof as set forth in claim 1.

21. A method for treatment of type 1 and 2 diabetes

mellitus, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, or a prodrug thereof as set forth in claim 1 alone, or in combination with another antidiabetic agent, an agent for treating diabetic complications, an anti-obesity agent, an antihypertensive agent, an antiplatelet agent, an anti-atherosclerotic agent and/or a hypolipidemic agent.

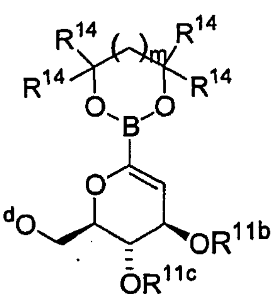
22. A compound of the formula:



(X)

wherein R^{11b}, R^{11c} and R^{11d} are each independently a protecting group for a hydroxy group, or an ester thereof.

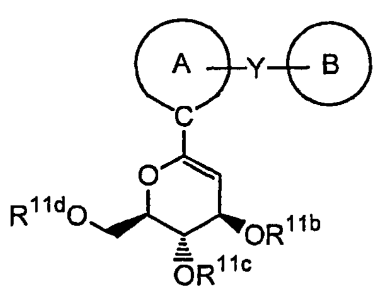
23. A compound according to claim 22, wherein the ester is the compound of the following formula:



(XI)

wherein R^{11b}, R^{11c} and R^{11d} are the same as defined in claim 22, and R^{14} is a lower alkyl group, and m is 0 or 1.

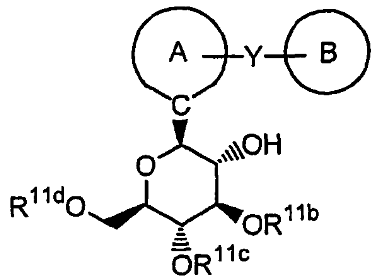
24. A compound of the formula:



(IX)

wherein Ring A, Ring B and Y are as defined in Claim 1, and R^{11b}, R^{11c} and R^{11d} are as defined in Claim 22.

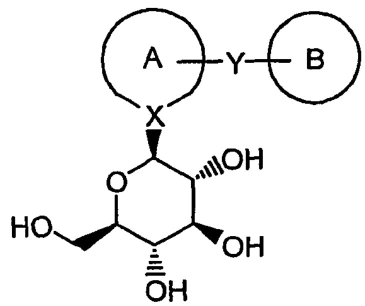
25. A compound of the formula (II-a):



(II-a)

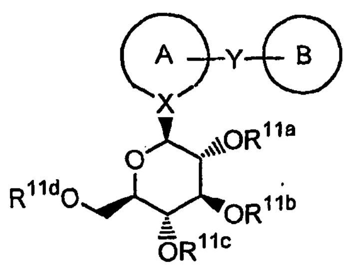
wherein Ring A, Ring B and Y are as defined in Claim 1, and R^{11b}, R^{11c} and R^{11d} are as defined in Claim 22.

26. A process for preparing a compound of formula I:



(I)

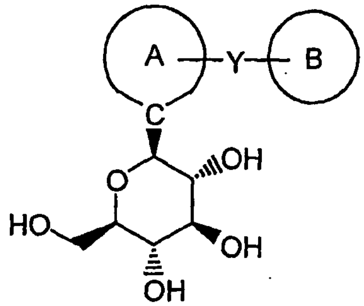
wherein Ring A, Ring B, X and Y are as defined in claim 1, which comprises deprotecting a compound of formula II:



(II)

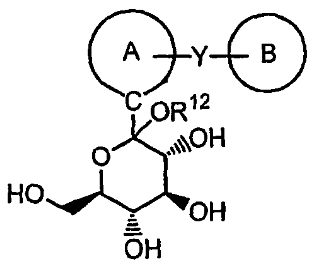
wherein Ring A, Ring B and Y are as defined in claim 1, R^{11a} is a hydrogen atom or a protecting group for a hydroxy group and R^{11b}, R^{11c} and R^{11d} are each independently a protecting group for a hydroxy group.

27. A process for preparing a compound of formula I-a:



(I-a)

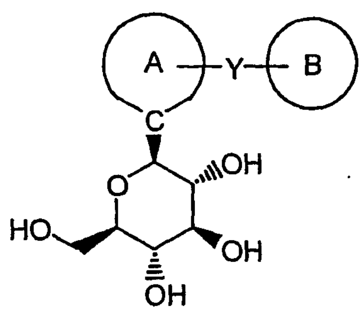
wherein Ring A, Ring B and Y are as defined in claim 1, which comprises reducing a compound of formula III:



(III)

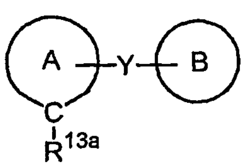
wherein Ring A, Ring B and Y are as defined in claim 1, and R^{12} is a lower alkyl group.

28. A process for preparing a compound of formula I-a:



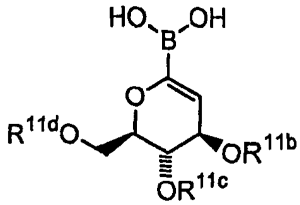
(I-a)

wherein Ring A, Ring B and Y are as defined in claim 1, which comprises coupling a compound of formula VII-a:



(VII-a)

wherein Ring A, Ring B and Y are as defined in claim 1, and R^{13a} is a bromine atom or an iodine atom, with a boronic acid compound of formula X:

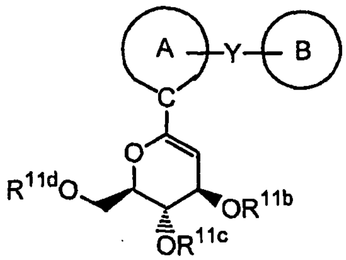


(X)

wherein R^{11b}, R^{11c} and R^{11d} are each independently a protecting group for a hydroxy group,

or an ester thereof,

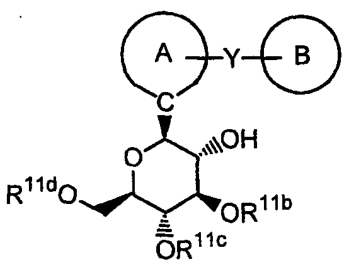
hydrating the resulting compound of formula IX:



(IX)

wherein the symbols are as defined above,

and removing the protecting groups from the resulting compound of formula II-a:



(II-a)

wherein the symbols are as defined above.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2004/011312

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AHMAD R ET AL: "SYNTHESIS AND STRUCTURE DETERMINATION OF SOME OXADIAZOLE-2-THIONE AND TRIAZOLE-3-THIONE GALACTOSIDES" NUCLEOSIDES, NUCLEOTIDES AND NUCLEIC ACIDS, MARCEL DEKKER, ANN HARBOR, MI, US, vol. 20, no. 9, 2001, pages 1671-1682, XP009039308 ISSN: 1525-7770 compounds 5A-5C,6A-6C	1-6,8, 18,25,26

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2004	25/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Klein, D

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZAMANI, KHOSROW ET AL: "Synthesis and structure determination of some new N-glycosides of 4,5-disubstituted-1,2,4-triazole-3-thiones " JOURNAL OF THE CHINESE CHEMICAL SOCIETY (TAIPEI, TAIWAN) , 49(6), 1041-1044 CODEN: JCCTAC; ISSN: 0009-4536, 2002, XP009039279 compounds 6(A-C),7(A-C)	1-6,18, 25,26
X	MAATOOQ G T ET AL: "C-p-hydroxybenzoylglycoflavones from citrullus colocynthis" PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 44, no. 1, January 1997 (1997-01), pages 187-190, XP004292916 ISSN: 0031-9422 compound 4	1-5
E	WO 2004/080990 A (IWASAKI FUMIYOSHI ; KOBAYASHI YOSHINORI (JP); KUROSAKI EIJI (JP); SHIR) 23 September 2004 (2004-09-23) the whole document	1-28
Y	GB 2 359 554 A (KOTOBUKI PHARMACEUTICAL COMPAN) 29 August 2001 (2001-08-29) the whole document	1-28
Y	US 2003/114390 A1 (SHER PHILIP M ET AL) 19 June 2003 (2003-06-19) the whole document	1-28
Y	US 6 562 791 B1 (HANDA SUKHDEV SWAMI ET AL) 13 May 2003 (2003-05-13) the whole document	1-28

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2004/011312

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			US	2001041674 A1	15-11-2001
US 2003114390	A1	19-06-2003	NONE		
US 6562791	B1	13-05-2003	NONE		